COLUMBIA UNIVERSITY

IN THE CITY OF NEW YORK

COLLEGE OF PHYSICIANS AND SURGEONS
DEPARTMENT OF SURGERY
AND
SCHOOL OF ENGINEERING
ELECTRONICS RESEARCH LABORATORIES

METHODS FOR DETERMINING BLOOD FLOW THROUGH INTACT VESSELS OF EXPERIMENTAL ANIMALS UNDER CONDITIONS OF GRAVITATIONAL STRESS AND IN EXTRA TERRESTIAL SPACE CAPSULES

STATUS REPORT P-1/168

NOVEMBER 1, 1960 TO APRIL 30, 1961

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Prepared for
Life Sciences Program
National Aeronautics and Space Administration
Washington 25, D. C.
Research Grant NsG-112-61

630 West 168th Street
New York 32, New York
and

632 West 125th Street
New York 27, New York

CU-1-61-NASA-112-PS/ERL

May 1, 1961

ABSTRACT

Work during the initial six months of this program has proceeded along three lines: (1) technical development of blood flowmeter instrumentation; (2) surgical considerations related to special problems of chronic implantation of flowmeter probes; (3) study of the relationship between levels of blood flow and organ activity.

Principal engineering effort has been focused on the fundamental phenomena operative in the flowmeter probe and on probe design. Two probes have been constructed and a third is nearing completion. A previously unrecognized source of zero drift has been discovered and corrected. Associated electronic equipment has been designed, assembled, tested and successfully employed in work on the several probes. A significant innovation which has been introduced is the use of a transformer coupled input for suppression of unwanted common mode signals. New low noise transistor amplifiers with characteristics suitable for space vehicle packaging are being developed. Linearity of the present apparatus has been found to extend at least into the near turbulent flow region.

Attention has been directed to the two vascular beds of physiologic interest that present particular problems with regard to chronic implantation of flowmeter probes, the myocardium and the liver. Surgical techniques have been perfected that will permit myo-

cardial and liver blood flow measurement. Two groups of animals have successfully undergone surgery and await the implantation of probes.

Studies of the relationship between organ blood flow and levels of physiologic activity have been initiated. The first organ system studied was the heart. For the first time autoregulatory mechanisms have been demonstrated within the myocardial vascular bed which rapidly and precisely maintain coronary blood flow at a level in keeping with the magnitude of cardiac work.

Following a summary statement of the status of the program, the work performed is described. A financial review of expenditures incurred and a proposal for future funding are appended.

AUTHORIZATION

The research summarized in this report was performed at the College of Physicians and Surgeons and the Electronics Research Laboratories of the School of Engineering, both at Columbia University and the Bell Telephone Laboratories, Murray Hill, New Jersey. This report was prepared by Robert F. Shaw, M.D. and Nathan B. Marple.

This project is sponsored by the National Aeronautics and Space Administration under Research Grant NsG-112-61.

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I. STATUS OF PROGRAM

This report summarizes progress during the initial six months of endeavor. As outlined in the initiating proposal, the goal of this project is the development of methods capable of furnishing a detailed profile of physiologic function in experimental animals in extra-terrestial space capsules and distant alien ambients through the medium of continuous measurement of blood flow to critical organ systems. Work has proceeded along three fronts toward the attainment of this goal: 1) the technical development of suitable blood flowmeter instrumentation; 2) surgical consideration of special problems related to chronic implantation of flowmeter probes; 3) study of the relationship between levels of blood flow and organ activity.

Following a summary statement of our progress and plans in these three areas, the work performed will be described. The final section is a statement of expenditures and a proposal for future funding.

A. TECHNICAL DEVELOPMENT OF BLOOD FLOWMETER INSTRUMENTATION

Because of the paucity of previous study of the complex physical phenomena operative in the function of an electromagnetic blood flowmeter, our work has progressed in step-wise fashion with considerable attention directed toward fundamental phenomena. The critical area in successful flowmeter design is the flowmeter probe in which the alternating magnetic field is generated and the electromagnetically induced flow signal is sensed. A major portion of our research efforts has been expended in this area.

Two probes have been fabricated and a third is under construction. The first probe was built to acquire experience in problems of magnet design, lead placement, potting, etc., and to allow initial experiments to be carried out. The second probe (Fig. 1) is arranged so that the flow section can be demounted, and has been employed as a "test bed" to allow effects of electrode and lead arrangement to be studied. The design of the third makes use of experience gained on the first two probes, and stresses efficient magnet design and small size. This probe is intended for implantation. Techniques designed to eliminate previously unrecognized spurious signals of capacitive and resistive leakages have been utilized in the construction of these probes.

In operation, the flowmeter requires electronic equipment to supply the magnet power, amplify the flow-modulated and reference signals, and recover the flow-signal modulation. This equipment has been designed, assembled, tested, and successfully employed in work on the several probes. A key component in this equipment is the so-called "balancer" which is employed to remove unwanted "transformer" voltages, and to recover the modulated flow signal in the presence of other disturbing signals such as muscle action voltages. A significant innovation which has been employed is the use of a differential transformer for suppression of unwanted common mode signals. This technique appears to offer greater and more stable suppression than can be obtained by electronic differential ammplifiers, and is highly resistant to overloading if these common mode signals are large.

Theoretical and experimental investigation of the operation of the balancer and differential transformer has revealed a possible source of "zero drift" not previously recognized. Common mode signals of carrier frequency may arise because of "transformer voltages" appearing in the loop formed by the signal elec-

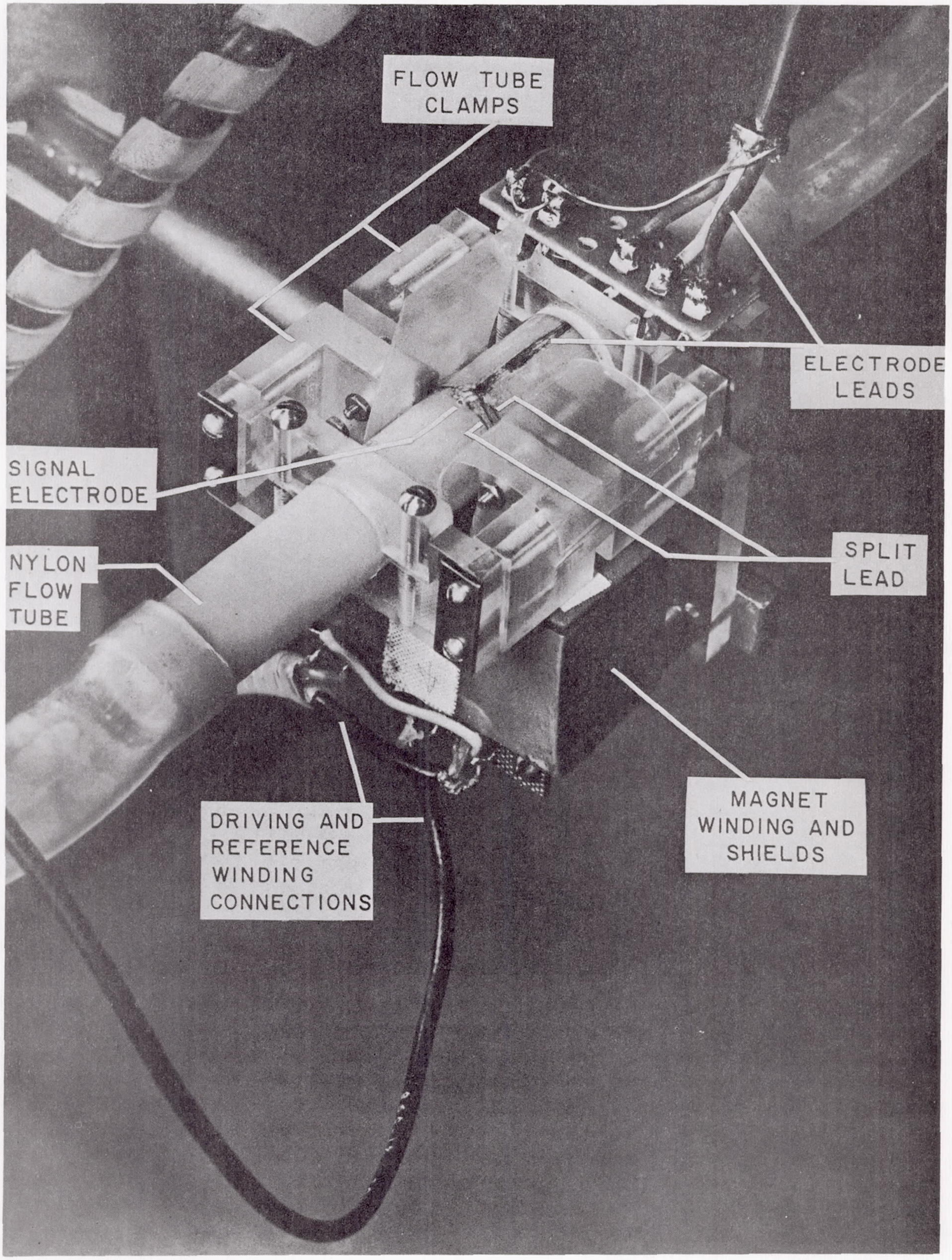

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Fig. 1 Probe Model 1

trode and ground leads. In a form of balancer which has been previously used, these signals are made equal in magnitude and phase (and hence rejected by common mode suppression) by adjustment of components of the balancer. Our analysis shows that stability of this balance is affected by cable lead capacitances which tend to be variable; shifts in these capacitances can lead to generation of spurious flow indications. By careful attention to electrode placement and lead arrangement, the common mode transformer voltage can be made very small, and this source of drift eliminated. Flow tubes employing these electrode and lead arrangements have been built, and the principles outlined above verified experimentally.

While present pre-amplifier design is satisfactory with respect to both gain stability and noise, it is at present the major noise source and is physically unsuitable for space vehicle packaging. Consequently, work is in progress on low noise transistor amplifier design with suitable power consumption characteristics, etc.

Measurements of flowmeter linearity have been carried out, employing saline as the fluid. (Fig. 2) These measurements were carried into the near turbulent flow region; no departure from linearity of the indications was detectable.

Continued research efforts will attempt further clarification of the factors influencing probe design. Work in this area will include continued investigation to improve understanding of phenomena occurring at the electrode-fluid interface, the effects of eddy currents in the fluid, effects on non-uniform magnetic fields, and asymmetric flow velocity distributions. Completion of the third probe under construction will permit investigations to be extended into situations in which the probe is surrounded by a conducting medium. It is expected that fabrication of a

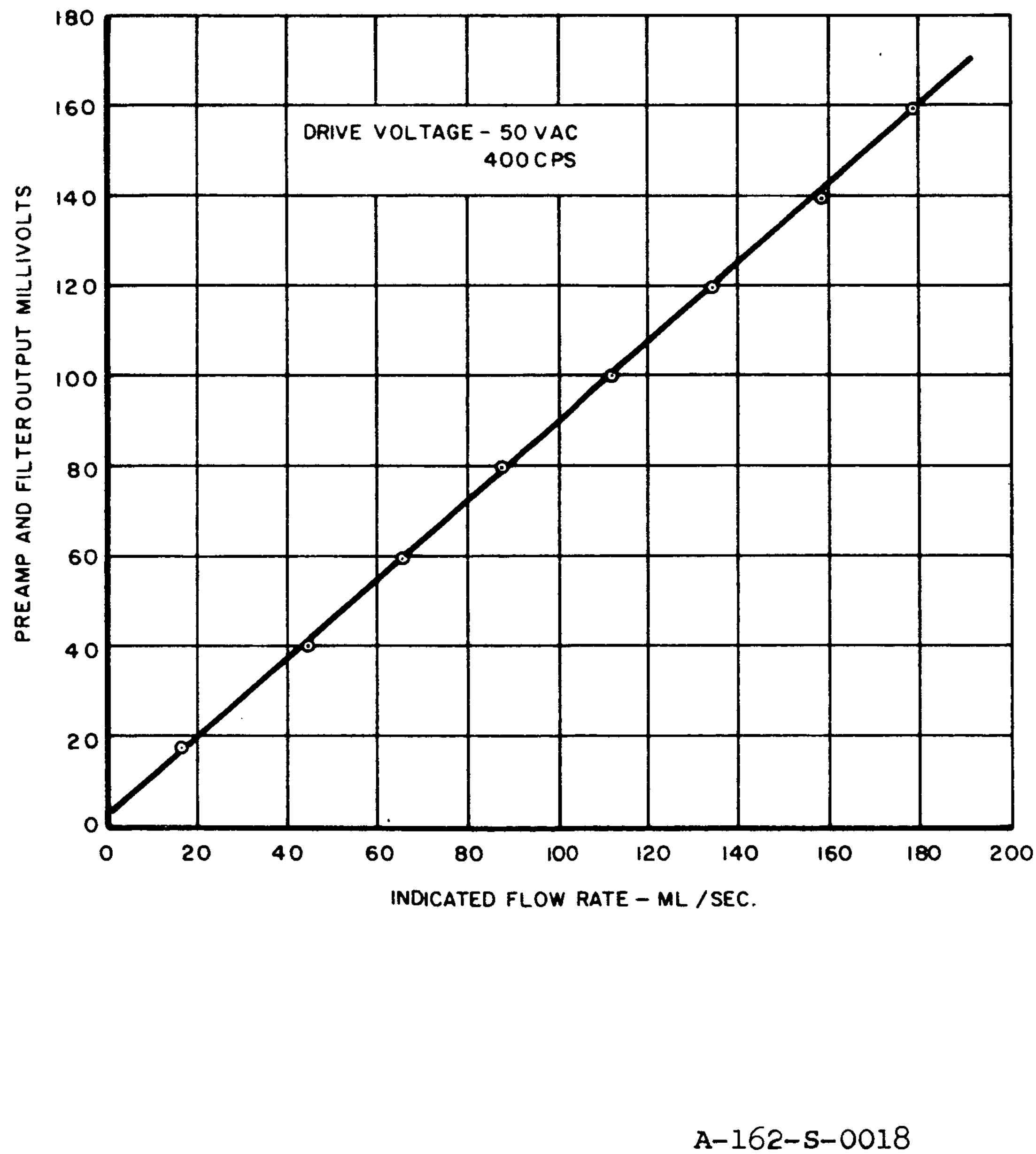

Fig. 2 Flowmeter Linearity

model of this probe will be completed shortly; it will then be used to investigate encapsulation techniques, electrode to winding leakage, current carrying capacity of the driving winding, etc. Results of these studies will be used in the fabrication of the third probe, which is expected to be completed by June 1. Initial testing of this probe will be done with saline; these results will be verified with blood. Following this, study of probe behavior under acute and chronic experimental conditions in the dog will be undertaken.

Design of probes for blood vessels of various sizes and various anatomic situations will be continued and extended. This work will include investigation of problems of fabrication, and the use of alternative magnetic designs. An attempt will be made to analyze theoretically the effects of nonuniformity of the magnetic field on the indications of the flowmeter. The importance of eddy currents, both within the blood vessel and external to it, will be studied.

Fabrication of a second set of electronic equipment for use in the physiologic laboratory will be completed. This will allow development testing of new probes in the engineering laboratory to continue independently of the testing and use of the instruments in the medical laboratory. Results of current investigation of low noise preamplifiers will be incorporated in this equipment. Studies of alternative magnet driving procedures are planned, with emphasis on design of a transistorized magnet driver, and possible use of feedback in the driver to obtain lowered flux distortion and improved long term amplitude stability. Eventually, an entirely solid state design for the electronic equipment capable of operation in a space vehicle ambient is desired. No serious problems are expected in this area and greatest efforts will be concentrated on probe design.

B. SPECIAL SURGICAL PROBLEMS OF IMPLANTATION

Flowmeter implantation techniques permitting the measurement of left and right heart output, myocardial blood flow, brain flow, liver and kidney flow, and peripheral muscle flows appear desirable. Of these most obvious sites of physiologic interest, only two present particular problems with regard to implantation. These are the myocardium and the liver.

Direct coronary artery implantation is not possible because of the site of coronary artery takeoff from the aorta at the base of the heart, the delicacy and abundance of significant branches of the coronary vessels and the intimate relation of these arteries to the vigorously contracting myocardium. The liver presents a special problem because it is unique in having a dual blood inflow via the hepatic artery and portal vein, and a venous outflow through large, very short channels directly into the vena cava. These two situations require special surgical preparation for flowmeter implantation. Appropriate surgical techniques have been under investigation.

The coronary artery problem has been solved by creating internal mammary-coronary artery anastomoses. (Fig. 3) A non-suture technique has been developed which permits good long-term results (85 per cent) in vessels of 2.5 mm and over. Through this technique, a longer arterial pathway to a major coronary artery is created, viz aorta→subclavian→internal mammary→coronary arteries. The left circumflex coronary artery is used in the dog because it is the major coronary vessel, carrying 45-60 per cent of coronary flow. Since all branches of the subclavian artery except the internal mammary are ligated, subclavian blood flow is, in fact, left circumflex flow. The hemodynamics of this longer pathway have been studied and demonstrated to introduce neither a time lag nor a limitation in flow, even with coronary flow rates ten times resting values. (Fig. 4)

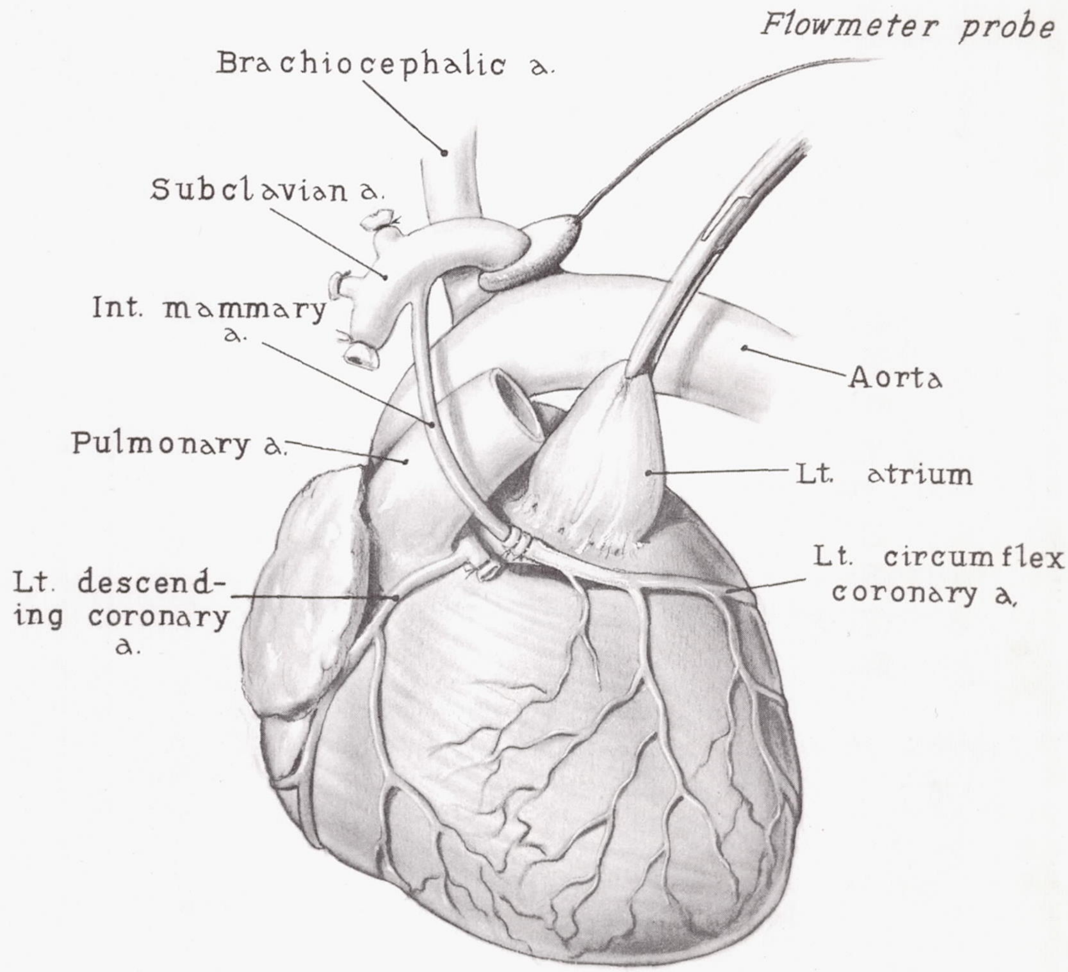

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Fig. 3 Internal Mammary→Coronary Artery Anastomosis for Measurement of Myocardial Blood Flow

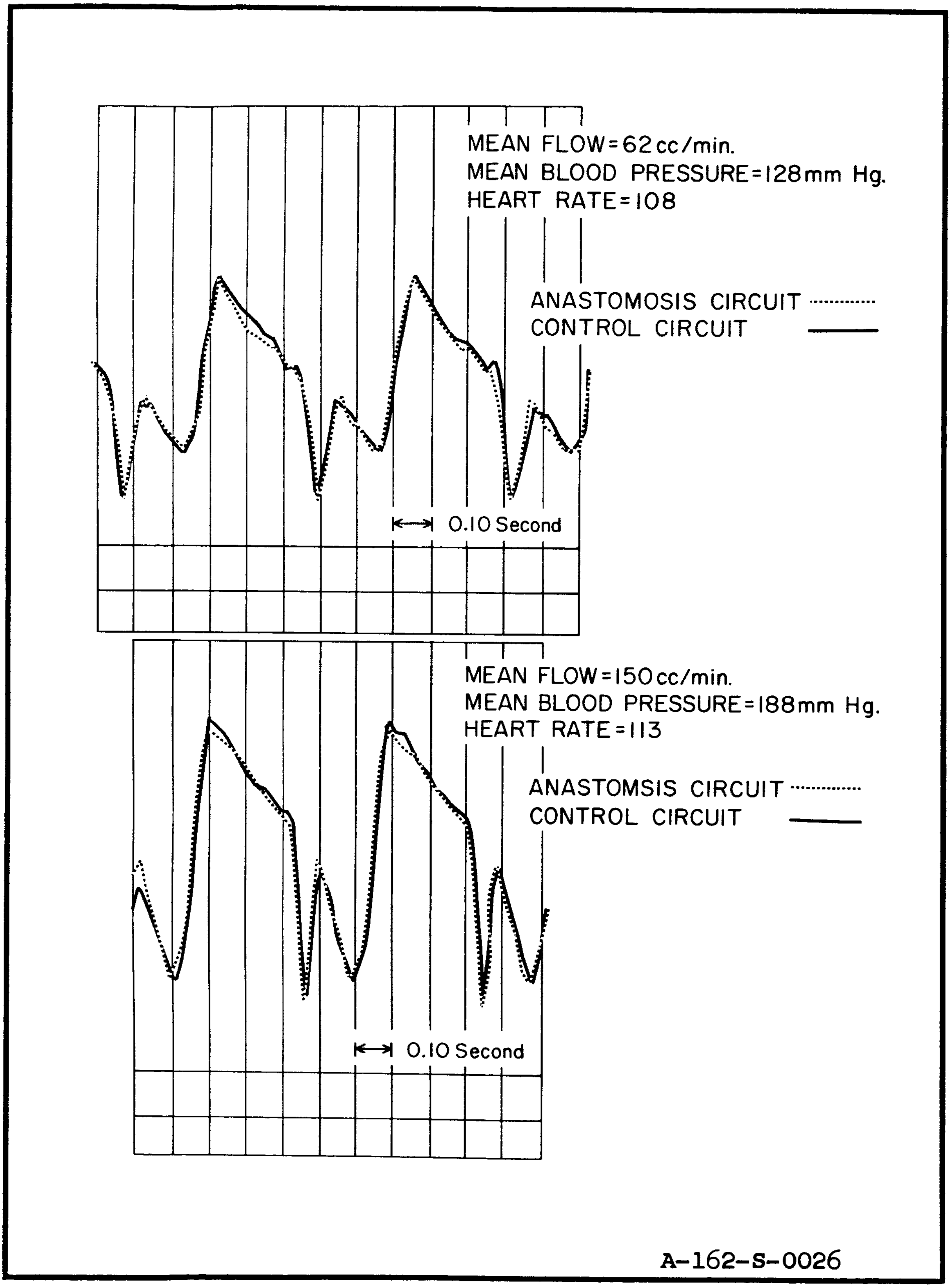

Fig. 4 Left Coronary Flow Via Normal Circuit Versus Internal Mammary Coronary Artery Anastomosis

The subclavian artery is a large artery firmly anchored at its base to the aorta and should be ideal for flowmeter implantation. A group of well over a dozen dogs have successfully undergone internal mammary-coronary artery anastomosis and are now many months post-operative.

The problem of monitoring liver blood flow has been attacked by utilizing a teflon prosthetic graft to bypass the inferior vena cava above the renal vein inflow (Fig. 5). In this manner, the thoracic inferior vena cava transports only the hepatic circulation and is of suitable length for flowmeter implantation. Five dogs have been thus far so prepared, the first of which is now two months post shunt. While it is still too early to be assured of long term patency, the technique looks promising.

Upon availability of implantable flowmeter probes and the second set of electronics (June-July), extended evaluation of flowmeter performance in acute in-vivo preparations will take place. Following this, techniques of implantation at various anatomic sites will be perfected. Considerable interplay between technical aspects of probe design and surgical demands for implantation is anticipated.

C. RELATIONSHIP OF ORGAN BLOOD FLOW TO LEVEL OF PHYSIOLOGIC ACTIVITY

In our original proposal, the following paragraph appeared:

> Of equal and possibly greater importance is the promise this method holds of furnishing a detailed profile of physiologic state even in difficult and far removed ambients. Through a complex of physiologic mechanisms that have evolved during the course of millions of years, perfusion levels of the various organs and tissues undergo constant subtle adjustments to meet the metabolic demands of organ activity. Monitoring of blood flow to various organs thus offers information concerning moment to moment organ activity and overall body economy.

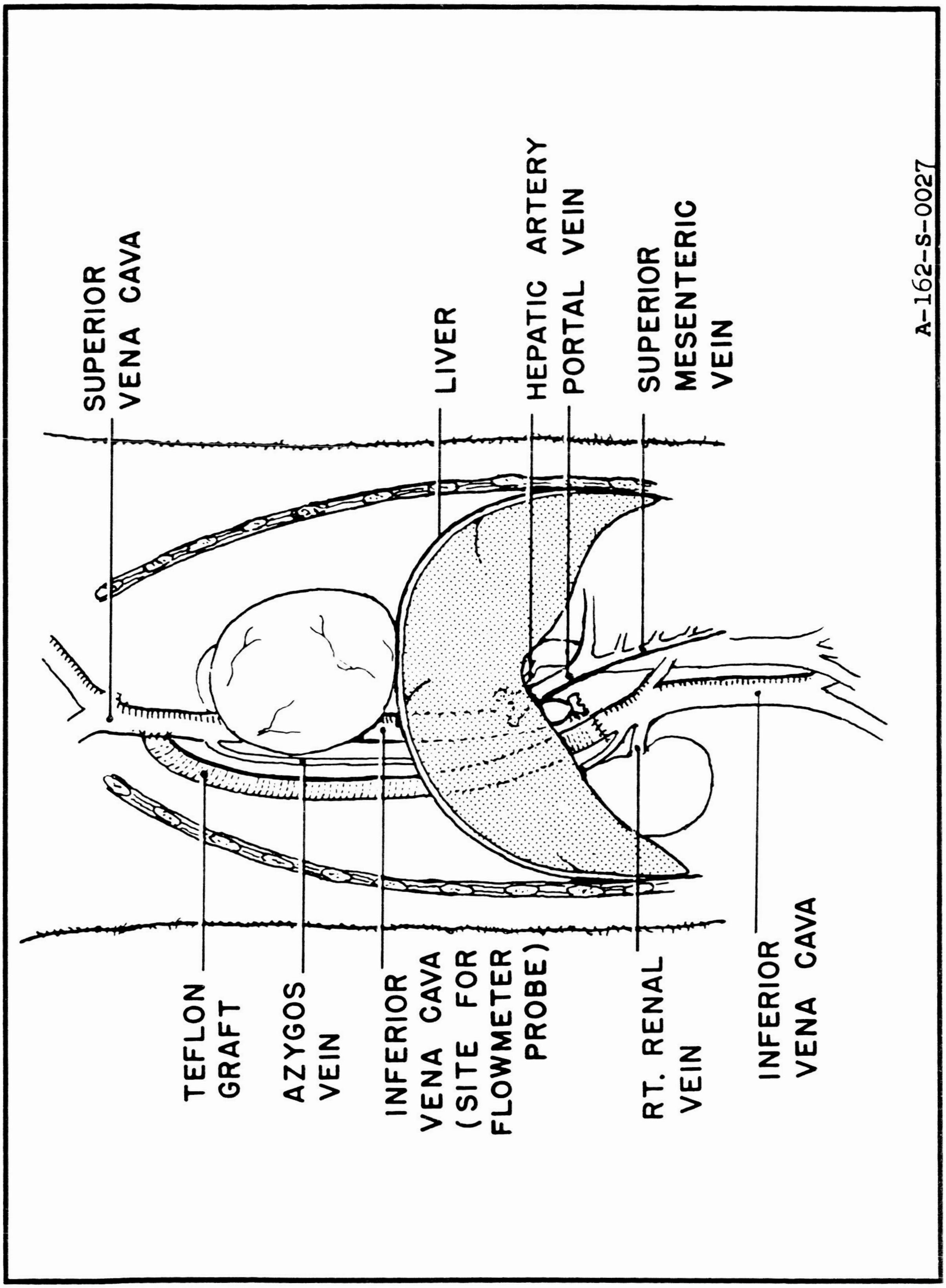

Fig. 5 Creation of Common Hepatic Vein for Measurement of Liver Blood Flow

This paragraph is an expression of an operational tenet we hold, a tenet supported by much indirect evidence but never subjected to direct investigation. To the extent to which this tenet holds rigidly true, the techniques being developed become enormously powerful tools for garnering information from experimental animals at great distances and in all manner of alien surroundings. Accordingly a systematic investigation of organ auto-regulatory mechanisms has been initiated.

We have begun study in this area with the myocardial vascular bed. The details of this study and the manner in which it is being performed will be appended as a later section. Our preliminary results in 13 experiments, however, suggest that the proposed tenet does hold strictly true within the broad physiological range that vasomotor activity is physically capable of regulating blood flow. Thus an experimental animal in a steady state with cardiac work held constant has a constant level of coronary flow. Imposition of sudden increments and decrements of coronary perfusion pressure is capable of increasing or decreasing flow only momentarily. Within a very few seconds, active vasomotor changes occur which return coronary flow to its former level. The level at which coronary flow is maintained is dependent upon the level of cardiac work.

Figure 6 demonstrates the auto-regulatory response to an increment and Figure 7, a decrement of coronary perfusion pressure; Figure 8 shows steady state pressure-flow curve plotted from a series of such altered perfusion pressures obtained experimentally. It will be noted that with variation in perfusion pressure, coronary flow is held constant within the capabilities of maximum vasoconstriction and vasodilatation of the bed. At extreme perfusion pressures above or below the "physiologic" range,vasoconstriction and vasodilatation are maximal and so resistance is fixed, the pressure-flow curve linear. Figure 9 shows an idealized curve for various levels of cardiac work.

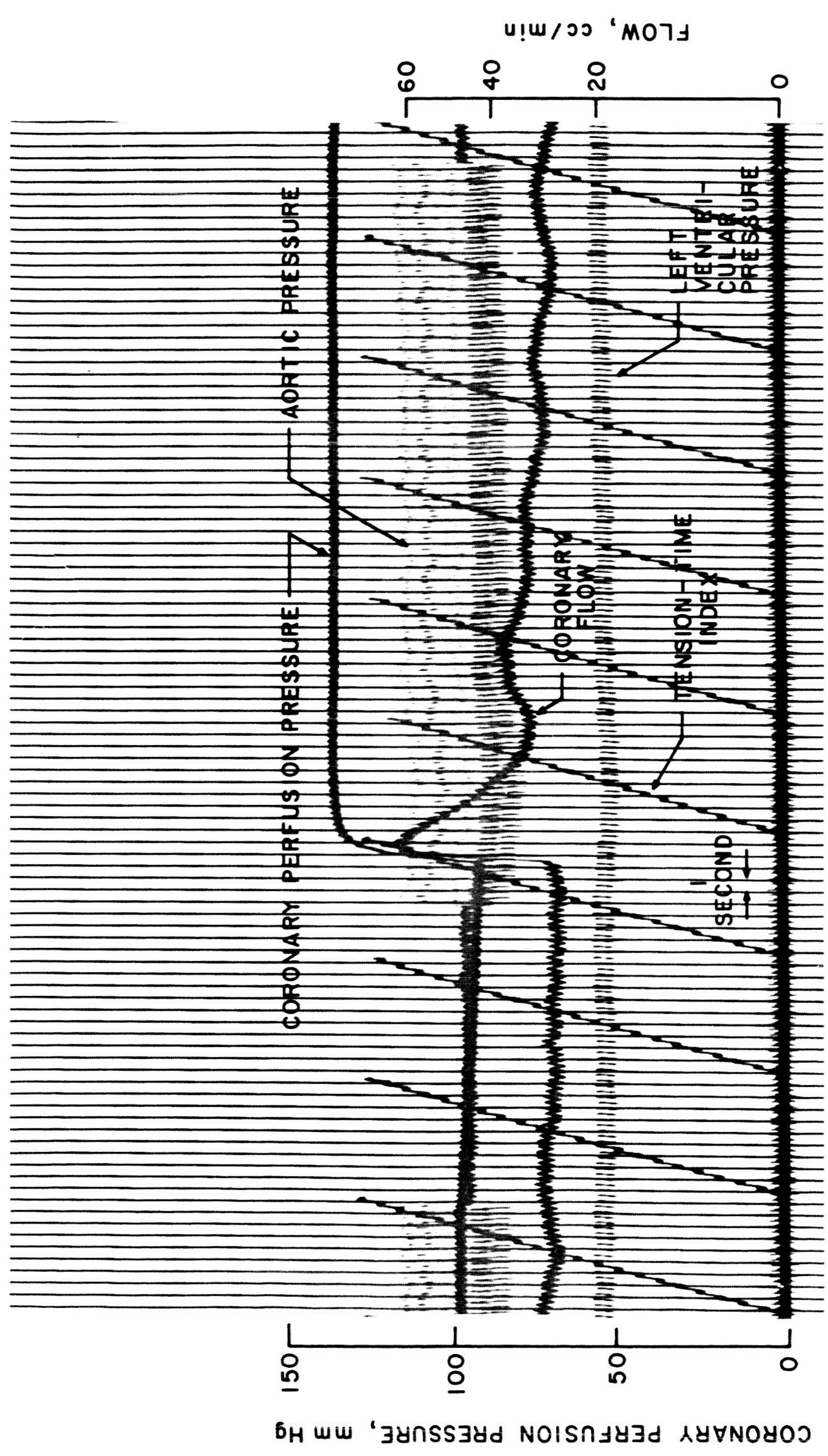

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Fig. 6 Coronary Flow: Transient Response to Sudden Increment in Perfusion Pressure

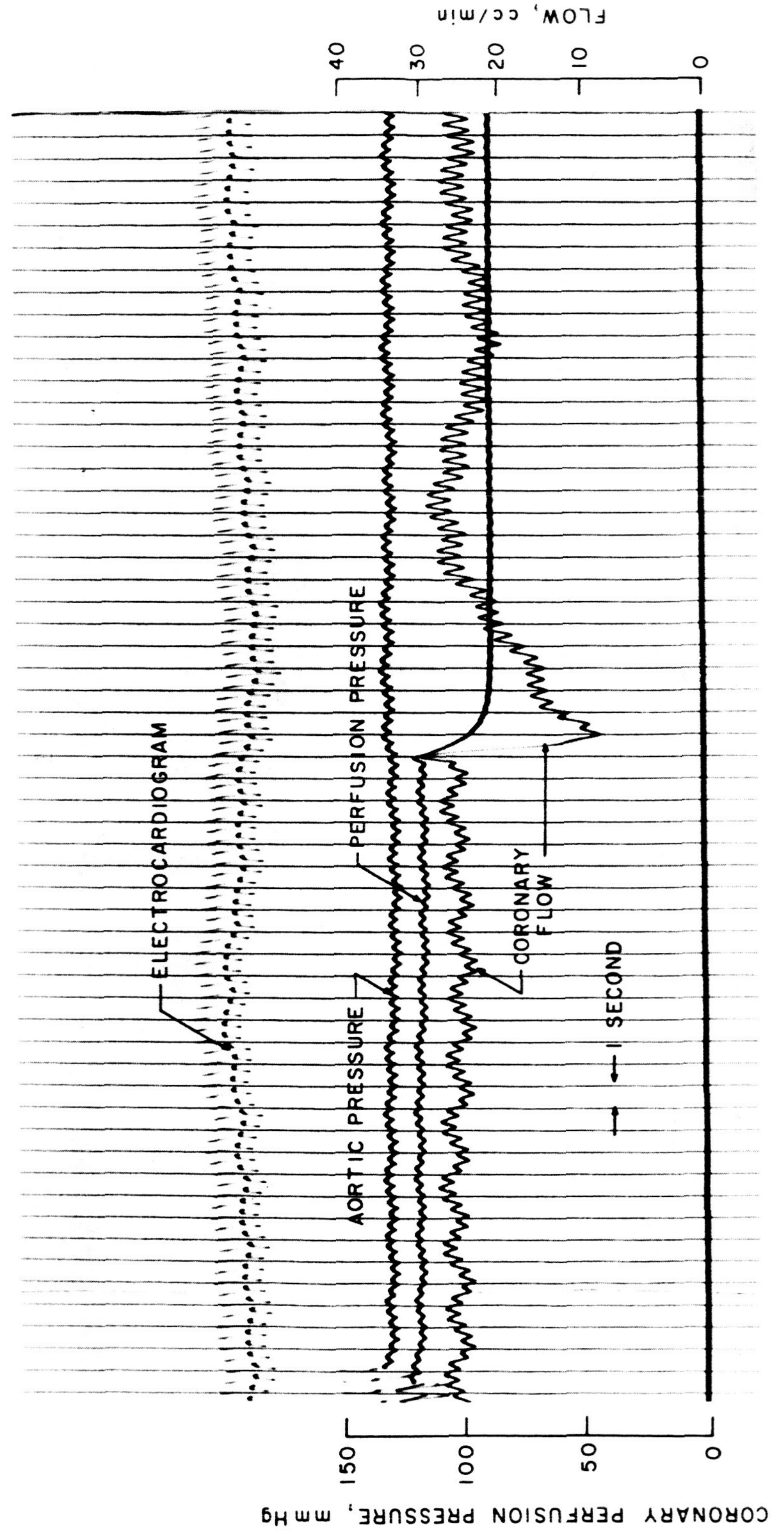

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Fig. 7 Coronary Flow: Transient Response to Sudden Decrement in Perfusion Pressure

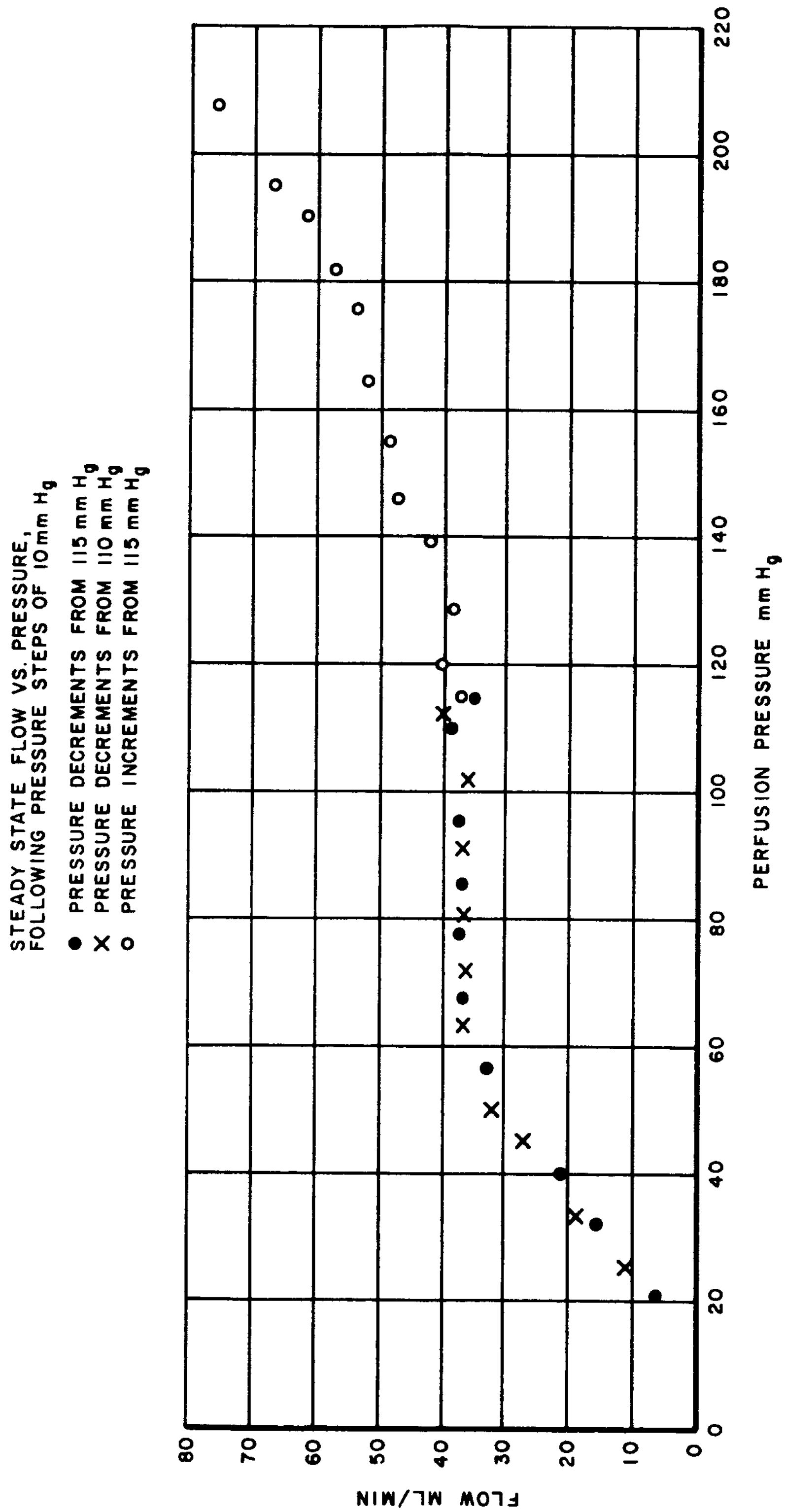

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Fig. 8 Steady State: Coronary Flow Versus Coronary Perfusion Pressure

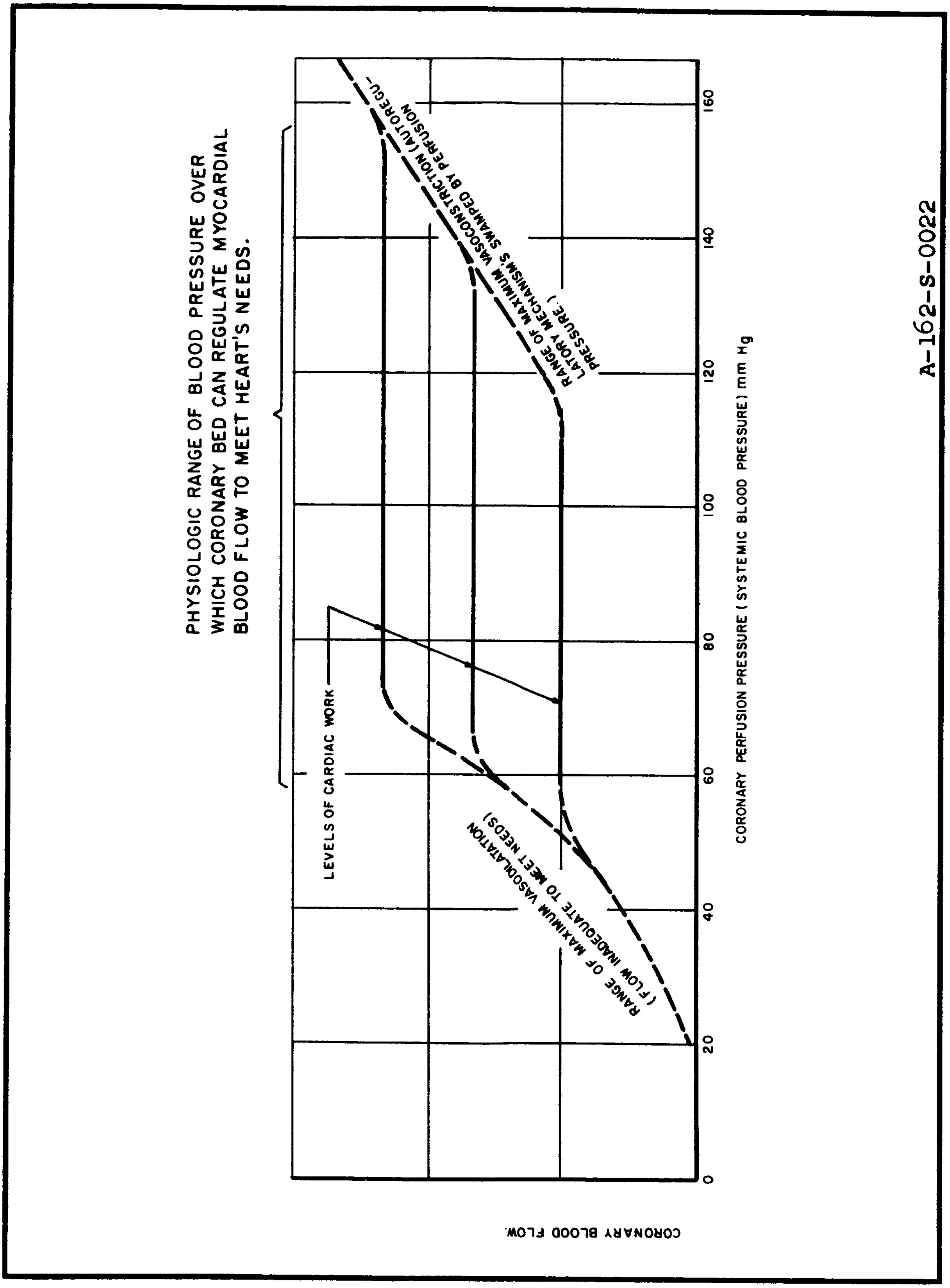

Fig. 9 Steady State: Idealized Curves, Coronary Flow VS Perfusion Pressure for Cardiac Work Loads of Different Levels

The implications of this work are exciting in terms of the larger goals of this project. Recent, as yet unpublished, work by Spencer and by Stainsby indicates that comparable auto-regulatory mechanisms are operative in the kidney and skeletal muscle. This work must be further refined and extended to study not only the other physiologically important vascular beds, but to relate blood flow to metabolic activity in the tissues, and to inquire into the feedback mechanisms by which such auto-regulation takes place. In this direction, we are turning our attention first to the metabolite, oxygen. Instrumentation has been set up for constantly recording arterio-venous oxygen difference by light absorption techniques which, coupled with flow measurements, will permit continuous measurement of oxygen uptake. Work will begin in July on the problems associated with continuous measurement of tissue oxygen concentration by polarographic micro-electrode techniques.

It should be noted that the techniques being developed offer promise of obtaining better information from experimental animals at enormous distances than we are now capable of obtaining in the laboratory or at the bedside with conventional techniques.

II. DESCRIPTION OF WORK PERFORMED

A. FLOWMETER DEVELOPMENT

1. Probe Design

a. The "Model Zero" Probe

The first probe built and tested employed a large C-shaped magnetic structure with a 10-mm gap. For convenience, this probe will be referred to as "Model O." The overall size of the probe is 1-1/4" by 1-1/2" by 1-3/4", as no attempt was made to miniaturize the test model. The core of the probe is made of a 6-mm thick stack of .004" thick hydrogen annealed vanadium permendur lamina. Two shielded drive coils, each consisting of 400 turns of #28 wire, are mounted on the legs of the C and two shielded 30 turn flux sensing windings of #40 wire are wound on the jaws. The unit is designed to give a flux density of 890 gauss in the gap with 1 ampere current in the drive coils. However, becaue of losses in the coil resistance, (8.31 ohm at dc) heating was excessive at this current and all tests were conducted at 1/2 amp drive.

The blood cuff is a teflon tube with a 6mm inside diameter on which are mounted six gold electrodes. Two of the electrodes sense the flow signal, the other four are grounds. The ground electrodes are located symmetrically in pairs up and down-stream in a plane perpendicular to the plane of the signal electrodes, which are centered between the jaws. One of the signal electrodes is connected to the electronic equipment through a split lead. The flux enclosed in the loop formed by the split lead induces a signal which is used in balancing the probe.

The drive coils are operated in series, with the center tap grounded. This connection is located near one of the signal electrodes, and grounding it materially reduced resistive leakage to the electrodes, especially during encapsulation. Since the uncured epoxy has a low bulk resistivity, leakage currents would otherwise completely unbalance the probe so that it could not be operated during curing. Because of the heat evolved during curing, and the differences in curing rates throughout the epoxy, small strains occur which displace the electrode lead wires and consequently unbalance the probe. To minimize the transformer component of the signal in this probe, it was found desirable to be able to make small mechanical changes in lead wire positions during curing, before the epoxy was completely hardened. This could only be done if resistive leakage from the drive coils to the electrodes was small.

The probe was tested for several months. Nonlinearity of flow signal vs. flow characteristic was too small to be measurable by simple means. Substitution of blood for saline as the fluid being measured had no noticeable effect. Zero drift was about .25 ml/sec per hour of operation and the unit often failed to return immediately to zero after flow. Recovery to zero took as long as eleven seconds, and residual error was observed to be as large as .25 ml/sec. Later experience has suggested that zero drift may have been caused by fluid leakage around the electrodes producing a partial short circuit, and circulating currents over the outer surface of the teflon tube. Both the electrode and wall materials are relatively soft. Teflon is subject to creep, and cannot be wetted by the epoxy. Under these circumstances it is difficult to achieve an adequate fluid seal or mechanical stability.

The potting material (Ciba epoxy 502) was chosen because it sets to a hard, dimensionally stable, machinable solid which is transparent to allow visual inspection of the probe after potting, and has almost no tissue reactivity. Unfortunately, its thermal conductivity is poor and with a heavy potting layer, central temperatures become excessive. The probe was finally destroyed when a shorted turn formed as the probe was coming to temperature equilibrium with 3/4 ampere of drive current.

b. The "Model 1" Probe

The design objectives for this probe were quite different from those of the preceding or subsequent probes. This probe, called "Model 1" for convenience, was designed to be used as a test piece with which certain basic phenomena could be observed and measured with reasonable facility. To achieve this, the probe was designed with a removable flow section so that various electrode configurations and lead arrangements could be checked.

The magnetic system of the probe is simple. The core consists of a 4-mm stack of .004-inch thick C-shaped lamina of hydrogen annealed vanadium permendur, with a 15-mm gap. The magnet is designed to produce a gap flux of 500 gauss with 1/2-ampere drive current. Two independent drive coils, each containing 572 turns, are layer wound on the legs of the C. Two eighty-turn flux sensing coils are wound on the legs of the C just below the jaws. The coils are shielded by end-rings and enclosed by a thin brass shield. All shields are split at appropriate points to prevent the formation of a shorted turn. No attempt was made to minimize size of the magnet structure.

The core is composed of interleaved short sections which are bolted together. This allows replacement of the jaw sections to test alternative configurations. The coils are wound on bobbins and may be conveniently replaced by alternative structures such as self cancelling coils which produce only small external electric fields. Design and construction of this magnet and that of the "Model 0" probe was carried out in collabration with personnel of the Bell Telephone Laboratories.

A magnet of this type is simple to fabricate but is not of minimum size and weight for the given gap flux, and is surgically awkward. It has a rather long magnetic circuit, which allows a very large leakage flux, raising the flux level within the core and requiring a large core for a given gap flux. This in turn increases the turn length of the windings, increasing the heating or the required wire size. Consequently the required window area is made larger, and the magnetic circuit becomes longer. As a result the magnet is a relatively bulky, heavy structure. Probes of this type are convenient for test purposes and may be used for extra-corporeal-flow measurement where small size and weight are not important, but are not suitable for implantation.

For initial experiments on the "Model 1" probe, the flow tube and lead arrangement shown in Fig. 10 were used. The flow tube is of teflon, while gold electrodes were chosen to minimize polarization and corrosion. The wires leading from the electrodes are crimped to the gold and led off to a terminal strip mounted on the probe. Signal electrodes are placed diametrically opposite each other, with the line joining them perpendicular to the magnetic field and to the direction of fluid flow. The ground electrodes, four in number, are arranged in diametric pairs 1/2" upstream and 1/2" downstream from the signal electrodes and lie in a plane perpendicular to the diameter joining the signal electrodes. The four ground electrodes are electrically connected to a common point. The outer signal

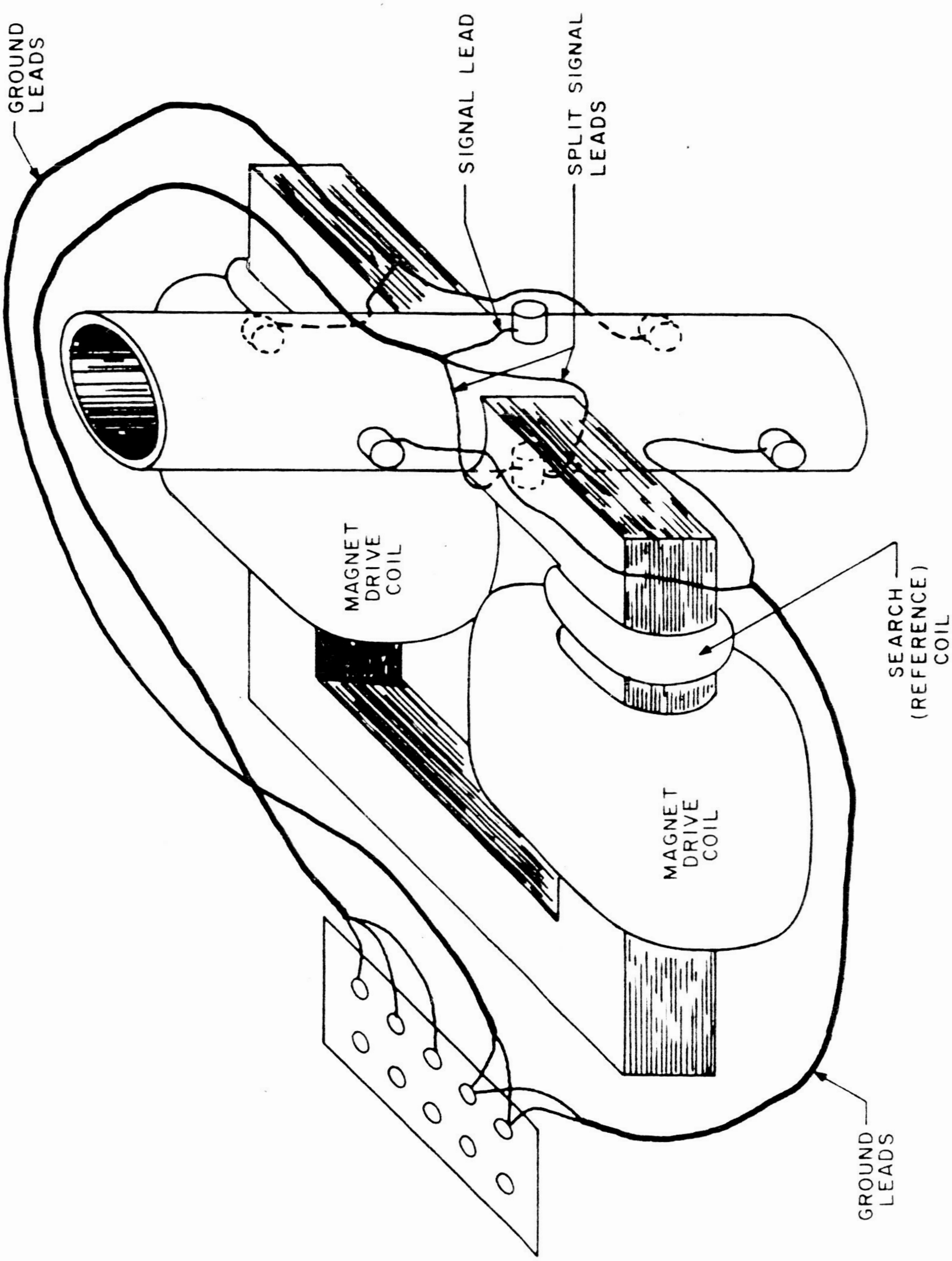

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Fig. 10 Electrode Lead Arrangement for Model 1 Probe with Teflon Flow Section electrode has a single lead, while two wires, forming "split leads", are brought out from the inner electrode around one of the magnet jaws.

A second flow section was designed for the "Model 1" probe. The flow tube is made of nylon, and stainless steel electrodes are employed. The electrode arrangement differs somewhat from that used on the first flow section. The signal electrodes have the same general arrangement, but only two ground electrodes are employed. These are located in the plane of the flow signal electrodes, diametrically opposite and displaced 90^{o} from signal electrodes. The electrode lead arrangement is also somewhat different. The split lead wires are brought from the electrode closest to the inside of the magnet structure in small machined slots, around the outside of the flow tube, passing close to the magnet jaw, and join the other signal electrode lead and the ground leads in a slot leading away from the upper electrode. The assembled probe, with the nylon tube in place, is shown in Figs. 11 and 1.

c. <u>The "Model 2" Probe</u>

The objective of this design is a probe of reduced size and weight, suitable for implantation. The weight of a probe for chronic implantation is critical, especially in the case of missile born animals where high "g" forces might be encountered.

A brief preliminary investigation showed that for a given gap width, a relatively small decrease in gap flux allowed a considerable decrease in size and weight. The equivalent input noise of the signal channel amplifiers currently in use is sufficiently low to allow a considerable reduction in the amplitude of the flow signals without significant degradation of performance. Therefore it was decided to build a miniature

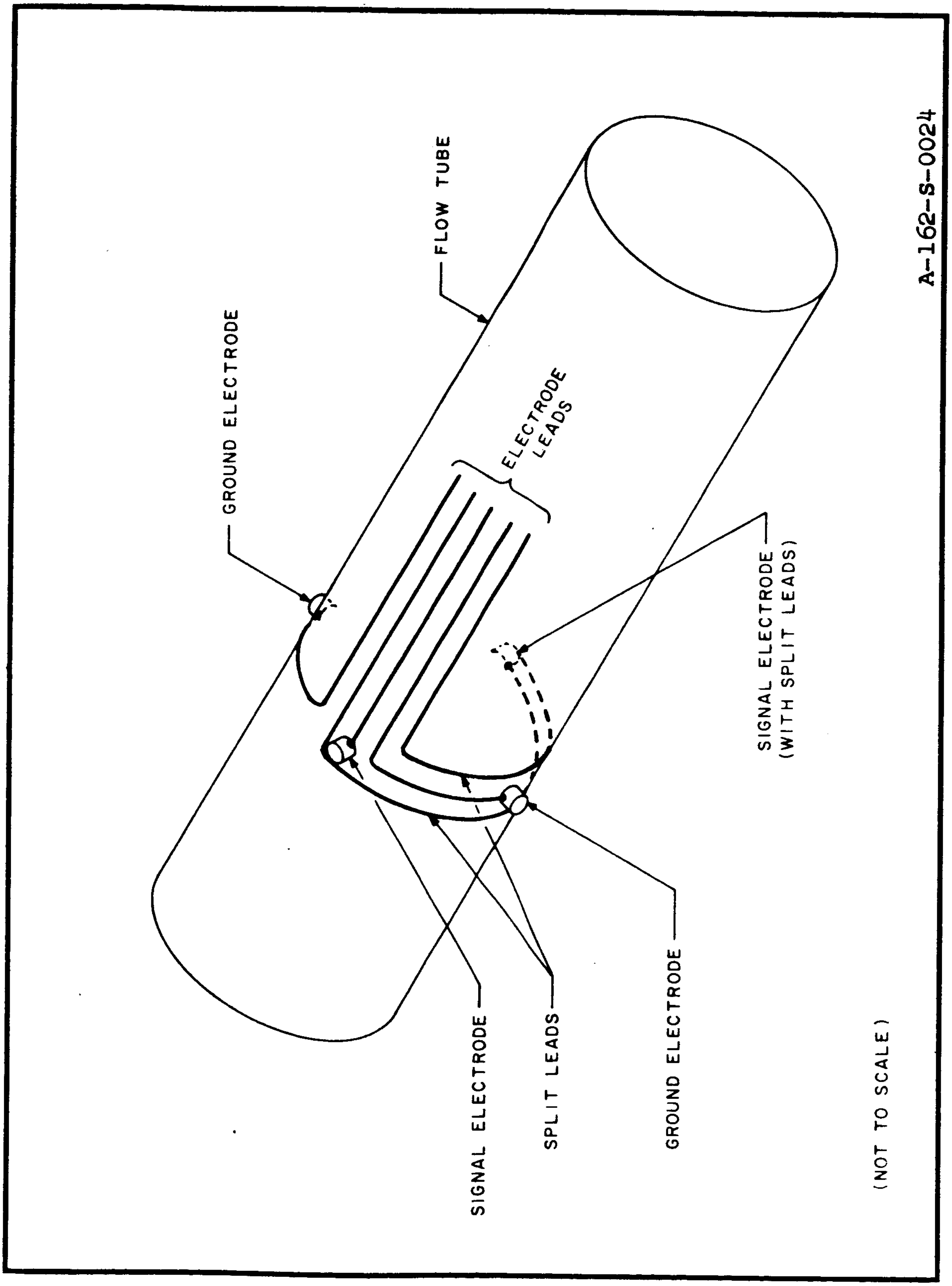

Fig. 11 Lead Arrangements to Minimize Ground Lead Induced Voltages

probe with a nominal field strength of 250 gauss, about half the flux density of the "Model 1" test probe. A gap width of 12 mm was selected, as the probe was intended for use with a dog aorta. For a flow voltage of $E = B\ l\ V \times 10^{-8}$, an average velocity in the dog aorta of 39 cm/sec, and an internal diameter of 10 mm, a mean signal level of somewhat under 100 microvolts is expected. With the signal channel amplifiers presently in use, the equivalent input noise in the frequency band of interest is about 0.3 microvolts, or less than 1 per cent of expected mean flow signal.

Neglecting the insignificant reluctance of the core, a gap of 12 mm and a field of 250 gauss requires an MMF of 278 ampere turns. Thickness of lamina stack has been set at 6 mm to obtain a relatively large region of uniform field. (All theoretical work on electromagnetic flow meters has been based on a uniform field and the effects of non-uniformity are at present unknown). Jaw area is thus about .72 cm^2, and, neglecting fringing, the total gap flux is about 200 Maxwells. Based on experience with the larger probes fabricated at Bell Telephone Laboratories, it is estimated that only about 10 per cent of the total core flux will pass through the gap. On this basis the highest core flux will be no more than 2000 Maxwells. This flux occurs at the part of the core farthest from the jaws. To limit the flux density at this point, a .2 cm^2 core cross section is needed. A 2.5 mm width is employed for the lamina at the base of the core, giving a .15 cm^2 cross section and a flux density of about 12,500 gauss, which is well below the saturation level for hydrogen annealed vanadium permendur. Since leakage occurs all along the core, the flux density decreases from center to jaw. Thus the core was tapered to 2 mm width behind the jaws. A further reduction in thickness is possible, but the lamina would be mechanically weak and difficult to assemble.

It is now feasible to fabricate subminiature, highly flexible multiconductor shielded cables capable of carrying up to 1/2 ampere. With 1/2 ampere in the drive coil, 557 turns are required to give the necessary MMF. Using a current carrying capacity of 1000 circular mils/amp, #26 wire is required.* Double nylon coated wire was selected for the driving winding to give maximum abrasion resistance with minimum loss of winding area.

A total of 406 turns in two separate coils were actually fitted in the space allowed for 557 turns. In addition, two eighty-turn auxiliary coils were wound on the core to sense the time derivative of the flux and provide a reference signal for the system. The sense coils are shielded by split endrings. The main drive coil is designed to be driven from the center out toward the poles and from the outside layer in toward the core to minimize the voltage on the coil ends nearest the signal electrodes.

The total driving winding resistance is under 1.3 ohms and the total power dissipation at 1/2 ampere current is less than 325 mw. Under the assumption that the surface area of the potted probe will be 4.5 in^2, dissipation will be 70 mw/in^2.

The thermal conductivity of the potting material controls the temperature gradient between the probe core and the surface and therefore the internal temperature. A low thermal resistance material is desirable to reduce internal temperatures. Since the jaws of the magnet will be in almost direct contact with the wall of a blood vessel, and the metallic lamina have a comparatively high thermal conductivity, the blood vessel may act as the main heat sink for the probe and will be subject

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* Copper area of 1000 circular mils/amp is conventional for transformer design, and very conservative in the present application.

to near maximum core temperature which must therefore be kept low. An additional advantage of a low thermal resistance encapsulating material is a more uniform heat distribution and surface temperature.

The blood cuff first designed for this probe was made of teflon, which has extremely low tissue reactivity. More recently, a new cuff has been made of nylon, which has comparable tissue reactivity and superior machinability, dimensional stability and rigidity. A .05-in. wall thickness is now ample to support the electrodes, which are countersunk flush to the outside of the cuff and cut flush to the inside. Electrode lead wires are nylon insulated and run in grooves in the wall of the nylon cuff. A method has been perfected to vacuum deposit an aluminum film on the surface of the nylon coating for shielding, if this becomes necessary.

Fabrication of this probe is in progress. A model of the probe core has been built and wound to check assembly methods. A photo of the probe without shielding or cuff is shown in Fig. 12. The cuff has been inserted and electrodes and lead wires placed. A satisfactory method for cold punching the core material has been worked out with a commercial stamping firm and the lamina are now being fabricated. Local arrangements have been made to hydrogen anneal the lamina to specification using a schedule supplied by Bell Telephone Laboratories.

Assembly and electrical testing of the new probe will begin within the next few weeks. Physiological testing will follow. Tentative design has been started on a 6-mm probe which will be modified on the basis of experience gained from the current probe.

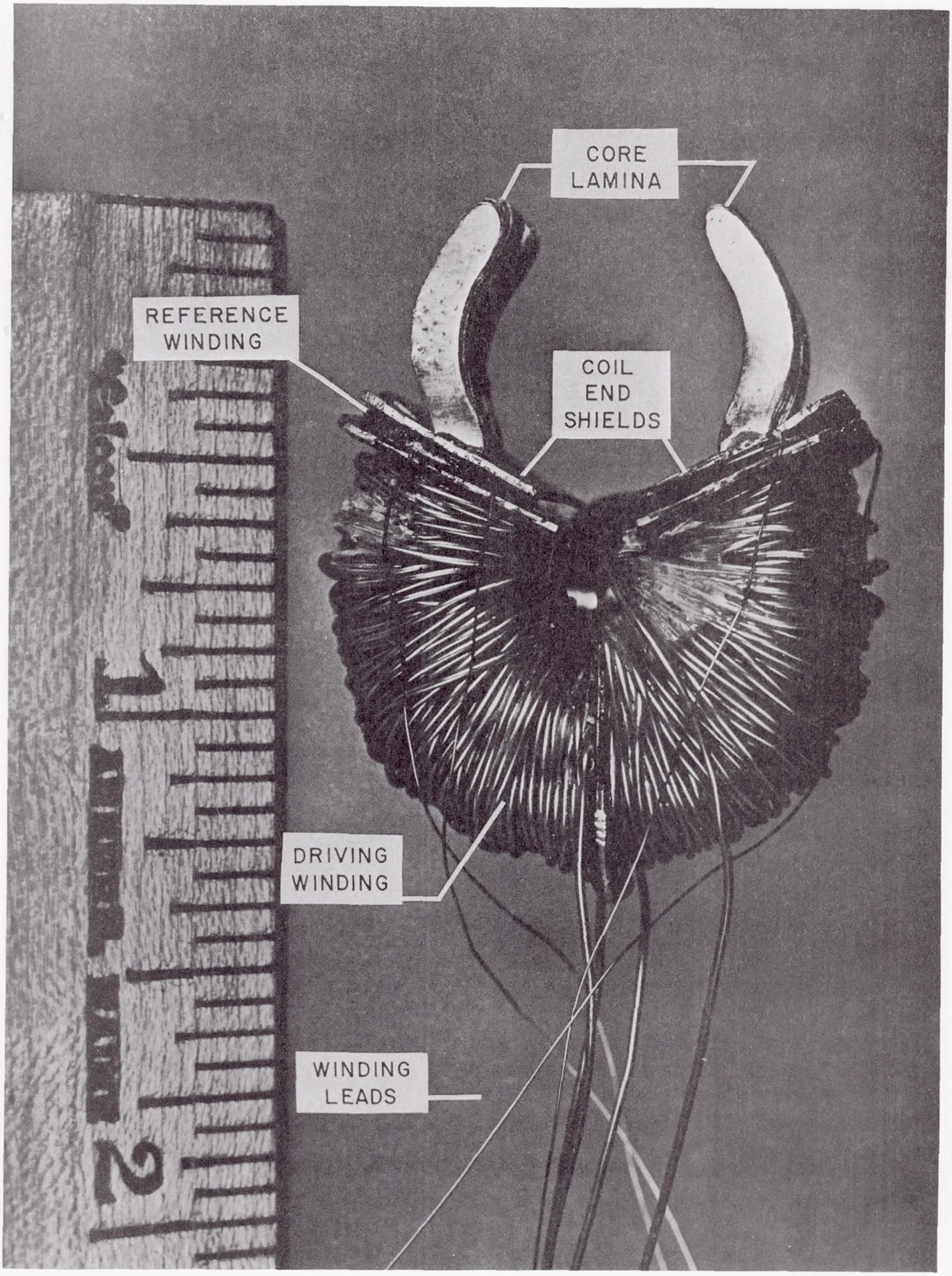

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Fig. 12 Probe Without Shielding

2. Circuit Arrangement and Electronic Equipment

Operation of a flowmeter probe requires various associated electronic equipment. As indicated in Figure 13, principal divisions of this equipment are the magnet driver, flow signal and reference signal amplifiers, and the phase sensitive detector. These components are discussed below.

a. Magnet Driver

The magnet supply now in use employs a Hewlett-Packard 206A audio oscillator which drives an Altec-Lansing 152A amplifier. The reactance of the magnet coil is compensated with a series capacitor, so that the amplifier load is resistive. There is a small resistor in series with the tuning capacitor so that the magnet coil current, as well as the voltage, may be easily measured.

b. Signal Channel

The arrangement of the components of the signal and reference channels are shown in Figure 14. The balancing network and differential transformer function together to eliminate or strongly suppress unwanted stray signals. Because of their importance in obtaining proper functioning of the flowmeter, these components have received considerable study, and their operation will be discussed at some length. Figure 15 shows the probable equivalent circuit of the electrodes, balancer and differential transformer. In this circuit, Z_1 and Z_2 represent the electrode surface to fluid impedance. Voltages E_2 and E_3 constitute the flow signal and transformer components of signals induced in the fluid. E_1 is the transformer voltage induced in the ground leads, while Z_5 is the ground electrode surface to fluid impedance. The resistances R_1, R_2, R_3, R_4 and R_5 comprise the physical components of the balancing system. How-

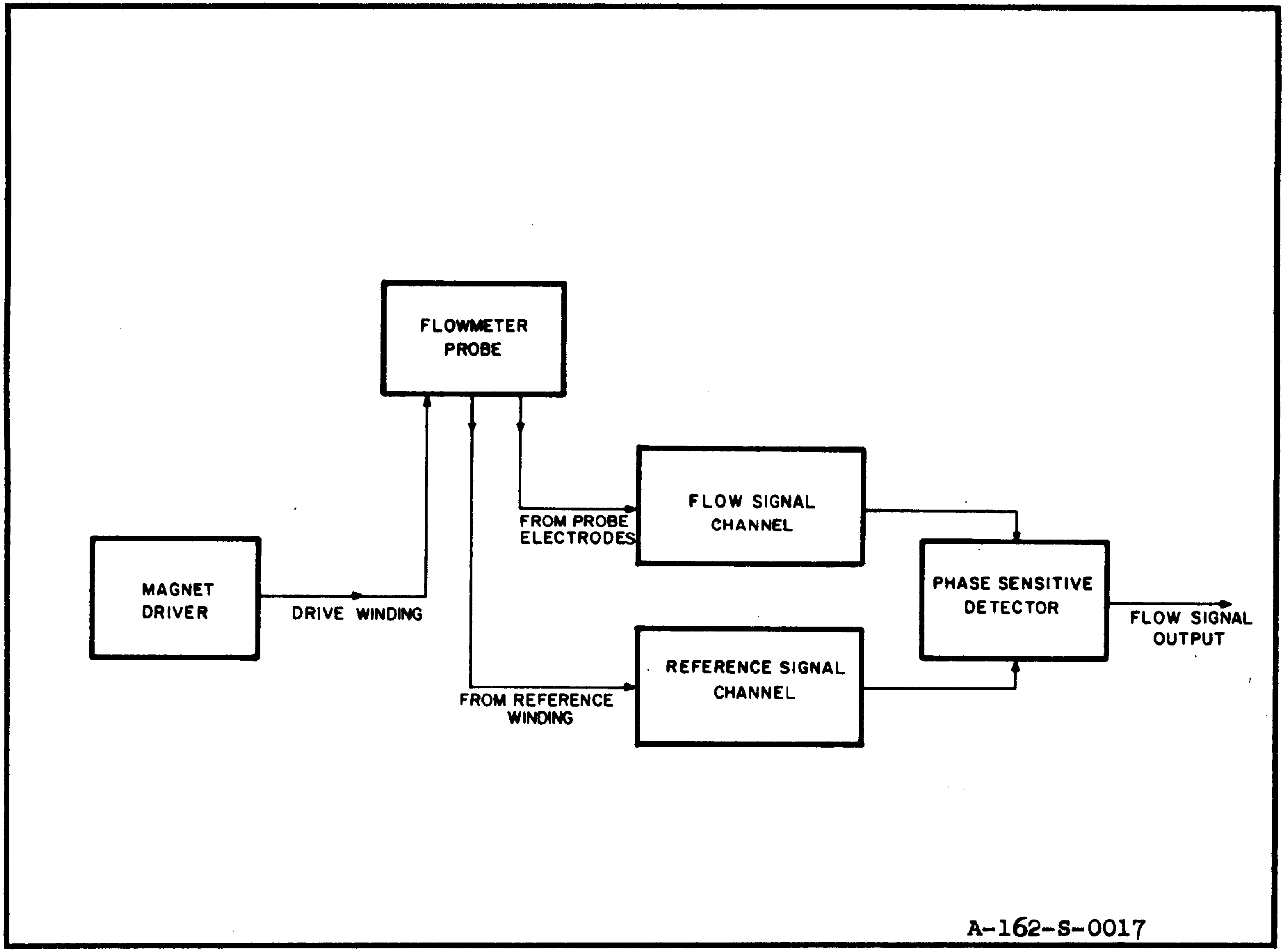


Fig. 13 Functional Components Associated with Flowmeter Probe

DRAWN	CHECKED	APPROVED

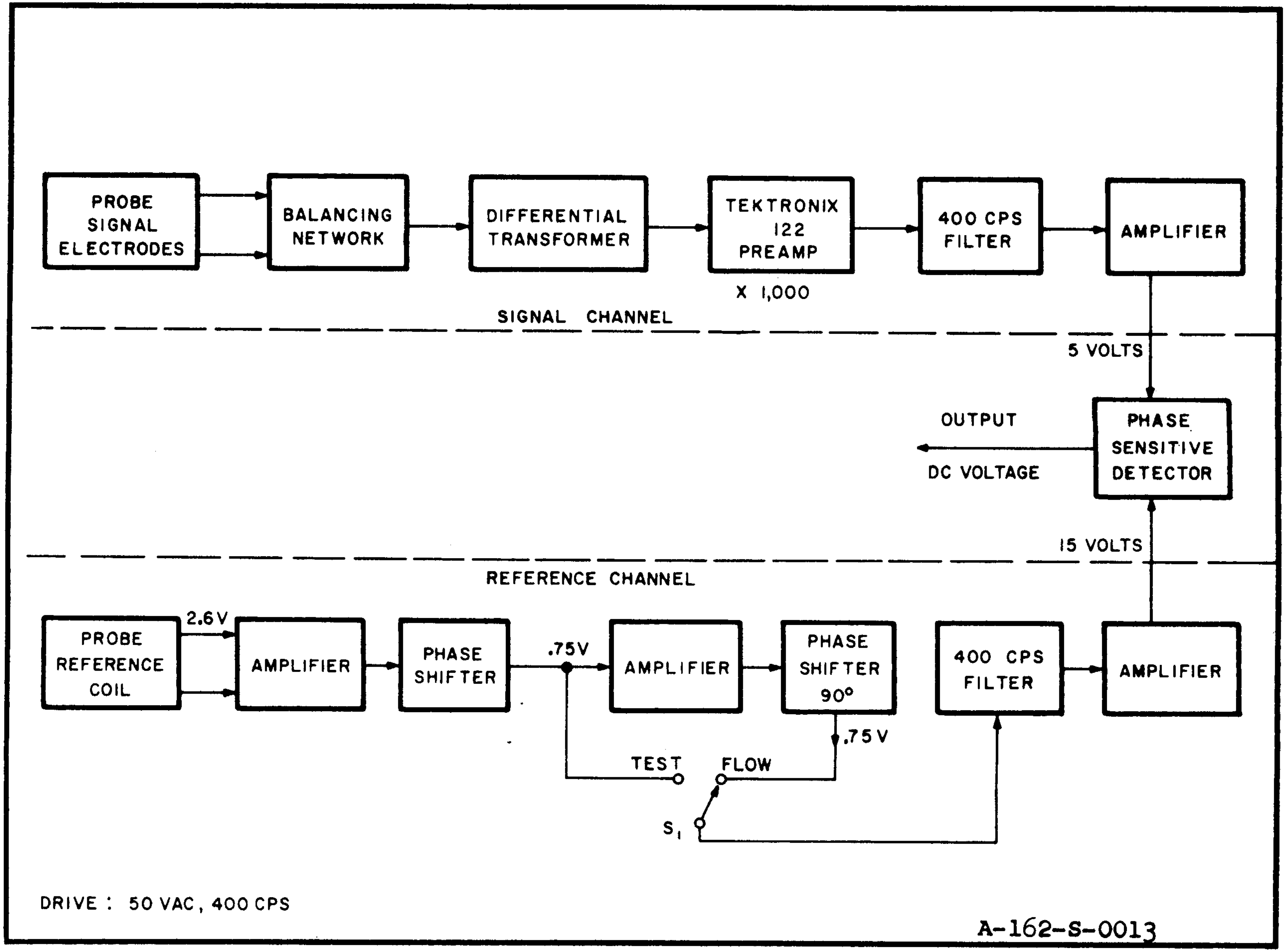


Fig. 14 Block Diagram of Signal and Reference Channel Components

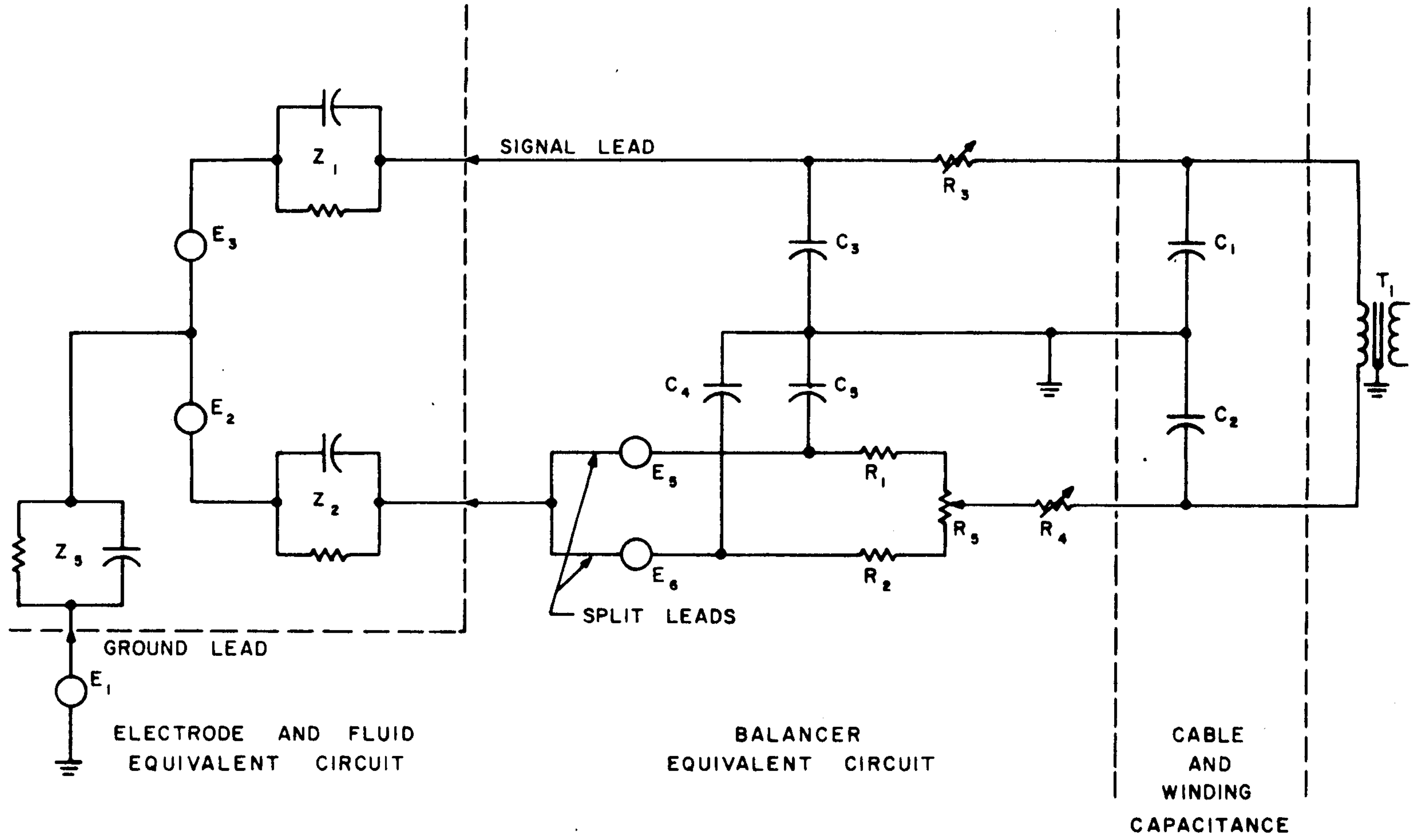


Fig. 15 Signal Electrode - Balancer Equivalent Circuit

ever, the balancer equivalent circuit also includes C_3, C_4 and C_5 which represent lead capacitances in the balancer and electrode cable. E_5 and E_6 are voltages magnetically induced in the split lead coming from one of the signal electrodes. Capacitances C_1 and C_2 represent cable and transformer winding capacitances, which are fairly large compared to the other capacitances, and somewhat variable. The equivalent circuit, thus outlined, is subject to modification as added knowledge is acquired.

When no flow is present, the voltage at the differential transformer secondary should be zero. This is accomplished by adjustment of R_5 until the net transformer voltage appearing around the loop containing the balancer arms R_4, R_5, the generators E_2 and E_3, and the differential transformer is zero. The ground lead transformer voltage, together with residual components of E_2 and E_3 which are in phase with the flux (and hence in 90° time phase with the transformer voltage), are however still present. These are eliminated by use of R_3 and R_4, which adjust the magnitude and phase of the residual voltage appearing across C_1 and C_2. When these voltages are equal, no net voltage difference appears across the differential transformer primary.

This balance, however, is dependent upon the values of C_1 and C_2, which are subject to change when the connecting cables are moved, etc. This causes the phase shift of the R_3C_1 and R_4C_2 combinations to vary. The best method to reduce the effect of changes in these capacitances is to make the voltage across them as small as possible. A major source of this voltage is the ground lead transformer voltage E_1 which may be reduced by carefully placing the ground and electrode leads so as to minimize the flux enclosed.

Measurements made with the electrode and lead arrangement shown in Figure 10 indicated that E_1 was as large as several millivolts, i.e. much larger than the flow signal itself. In this case, a change of the capacitances C_1 or C_2 of even a few micro-micro-farads produced a significant imbalance. The second flow tube (Fig. 11) was then designed and constructed so that E_1 was minimized. When this flow section was put into use with the Model 1 Probe, effects of change in C_1 and C_2 were investigated and found to be no longer significant.

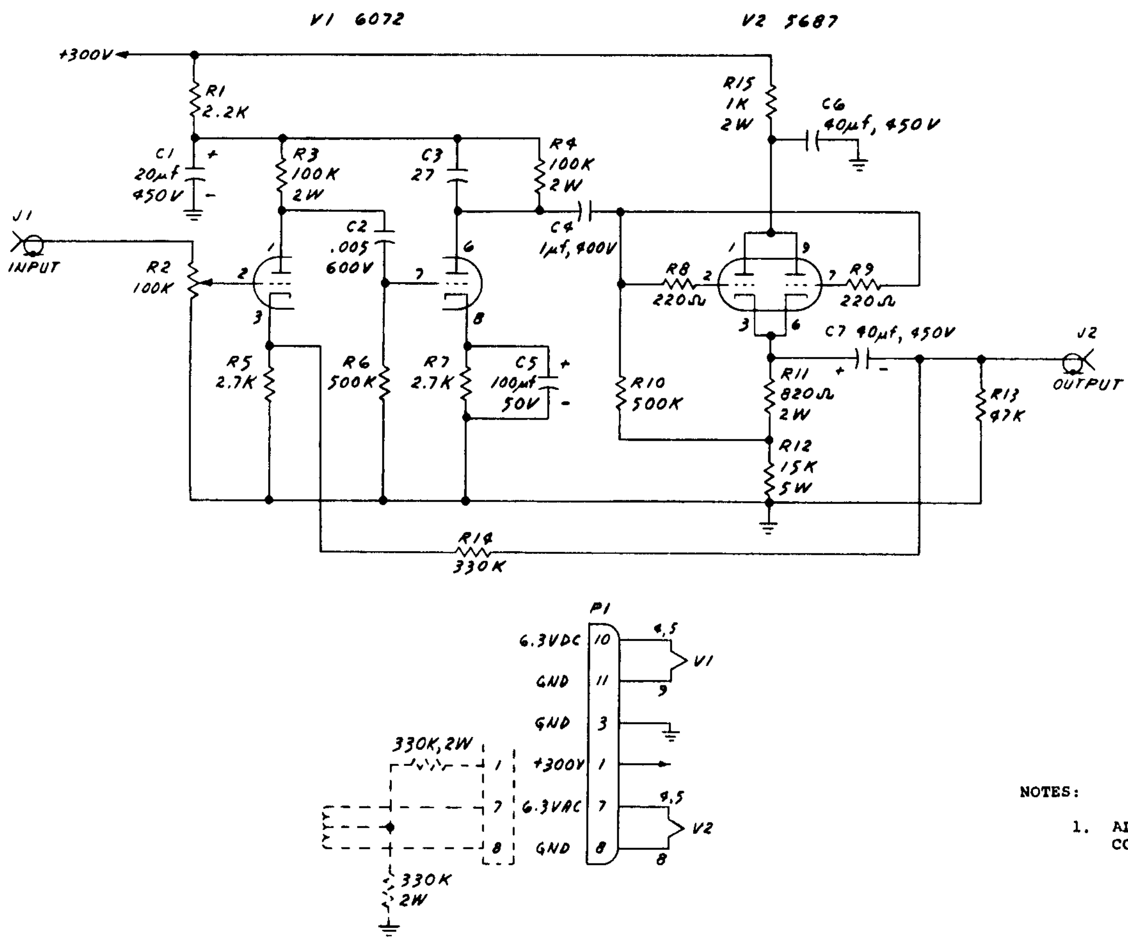
In initial tests a differential transformer was not employed; common mode rejection was obtained in the differential preamplifier. However, the amplifier adjustment which produced maximum common mode rejection was found to drift with time. Similar changes were produced by large input transients. Therefore it was decided to investigate a transformer coupled input with a "floating" transformer primary acting as a common mode rejection device. This system has the advantage of being stable, and allowing use of a relatively simple single ended preamplifier.

A James Type 2100 differential transformer was selected for detailed tests. The unit contains four separate, identical, independently shielded windings and may be used in a variety of configurations. The circuit finally selected employs the two primary windings in series, and their shields connected to the input leads. The core, case and secondary shields were all grounded and the secondary windings were run in series with one end grounded. The common mode rejection was then measured to be 93 db with no resistance in the primary circuit, and 89 db with a 10 K imbalance. By comparison, common mode rejection of the Tektronix amplifier is about 70 db.

Operation of the flowmeter depends on the input impedance of the signal channel being very much larger than the impedance of the fluid between the electrodes if variations in the impedance of the blood due to temperature, blood chemistry, etc. are not to affect the performance significantly. The input impedance of the transformer is guaranteed to be 630 K or more at 60 cps and almost 4 megohms at 400 cps with the secondary open. This is ample for our purposes. The transformer shielding is sufficiently good that no 60 or 400 cps pickup is observable with the primary circuit open.

Output of the differential transformer is fed to a Tektronix Type 122AR low noise preamplifier having a gain of about 1000, which raises the flow signal to a more usable level. The preamplifier is followed by a bandpass filter (Burnell Type S-2531) having ($\pm$ 60 cps) bandwidth centered about 400 cps. The filter strongly rejects 60 cps power frequency pickup, harmonics of the 400 cps flow signal (which may arise due to distortion of the magnet flux waveform), and noise arising in the preamplifier.

Further amplification is carried out after the filter to raise the signal to a level suitable for operation of the phase sensitive detector. The amplifier which is employed was designed for general purpose use wherever gain or isolation was needed. As indicated in Figure 16, two cascaded resistance coupled stages employing a type 6072 low noise twin triode are followed by a cathode follower. To reduce output impedance and distortion, and improve gain stability, feedback is employed around the entire unit. Open loop gain is about 680; gain with feedback is about 100. Closed loop frequency response is substantially uniform from 20 to 20,000 cps, so that phase shift in the region about 400 cps is very small. The closed loop equivalent input noise is about 3 microvolts (wideband). Input impedance is 100 K, output impedance 7.5 ohms. A gain control is provided outside the feedback loop to adjust amplification.



COMPONENTS LISTS

C1	20 μf	450V
C2	.005 μf	600V
C3	27 μμf	MICA
C4	1 μf	400V
C5	100 μf	50V
C6,7	40 μf	50V

J1,2	BNC.	COAXIAL CONNECTOR
P1	11 PIN	AMPHENOL CONN. NO. 26-809

R1	2.2K	
R2	100K	LINEAR
R3	100K	2W WELWYN
R4	100K	2W
R5	2.7K	WELWYN
R6	500K	
R7	2.7K	
R8,9	220 OHMS	
R10	500K	
R11	820 OHMS	2W
R12	15K	5W
R13	47K	
R14	330K	WELWYN
R15	1K	2W
	330K	2W

V1	6072
V2	5687

NOTES:

1. ALL RESISTORS ARE 1/2 WATT, 10%, CARBON COMPOSITION EXCEPT AS NOTED. K= 1,000 OHMS

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Fig. 16 General Purpose Amplifier - Schematic Diagram

The preamplifier currently in use (Tektronix 122AR) is satisfactory with respect to both gain stability and noise. However, it is rather bulky, must be battery operated and has a maximum gain of only 1000. A gain of 10,000 would be considerably more convenient. It was decided to design a more suitable preamplifier as part of the second electronic system being assembled for use in the physiological laboratory. The new amplifier will be single ended, since success with differential transformer input configuration eliminates the need for a differential input stage. Although the noise characteristics of the present preamplifier are satisfactory, it is at present the major noise source. The effect of noise is to reduce the ability of the system to resolve small flows. Thus it was decided that the new preamplifier should be made as quiet as possible using relatively conventional techniques.

The major source of noise in the preamplifier is that which arises in the first stage. This noise arises (a) from fluctuations in the plate current arising from variations in the space charge distribution (b) "flicker noise" due to uneven electron emission from the cathode, and (c) microphonism. The spectrum of noise arising from the first source is uniform in the range of frequencies of interest. For a triode, the equivalent noise input resistance due to this type of noise is approximately $2.5/g_m$. Thus this noise is reduced by increase of transconductance. The spectrum of flicker noise is variable among tubes of different types but increases rapidly with decreasing frequency and increasing cathode current. Since high transconductance usually also requires high cathode current, reduction of this source of noise may tend to increase that due to the first source. Microphonism varies widely among different tube types, and depends principally on the rigidity of the mechanical structure of the tube.

Experiments are in progress to develop a satisfactory low noise first stage. The first circuit investigated used a 5687 triode operated at moderate plate voltage and current. The 5687 gave a fairly high transconductance in the test circuit, but proved to have a very high microphonic sensitivity. Several tubes were tested and the results were uniformly unsatisfactory.

The second attempt was planned around a stacked ceramic tube which combines excellent transconductance with remarkable immunity to mechanical perturbation. This class of tubes is designed to deliver excellent noise figures in the UHF region, and a preliminary investigation showed that no particular attention is paid to flicker noise in their design. The tubes are extremely variable in this respect and generally not satisfactory.

The third test involved a type 6072 "low noise" triode operated with abnormally low plate voltage. This approach seems promising. The observed noise was comparable to that of the Tektronix amplifier, and was predominantly 60 cps pickup. The test unit is now being shielded and further tests will be conducted.

Concurrently, work was begun on a low noise transistor amplifier suitable for operation under adverse ambient conditions and requiring a minimum of power. The input stage uses a low noise, ultra low leakage npn silicon planar transistor which allows high input impedance together with minimum noise current supplied to the input network from the amplifier. Preliminary results with this unit are very promising.

c. Reference Channel

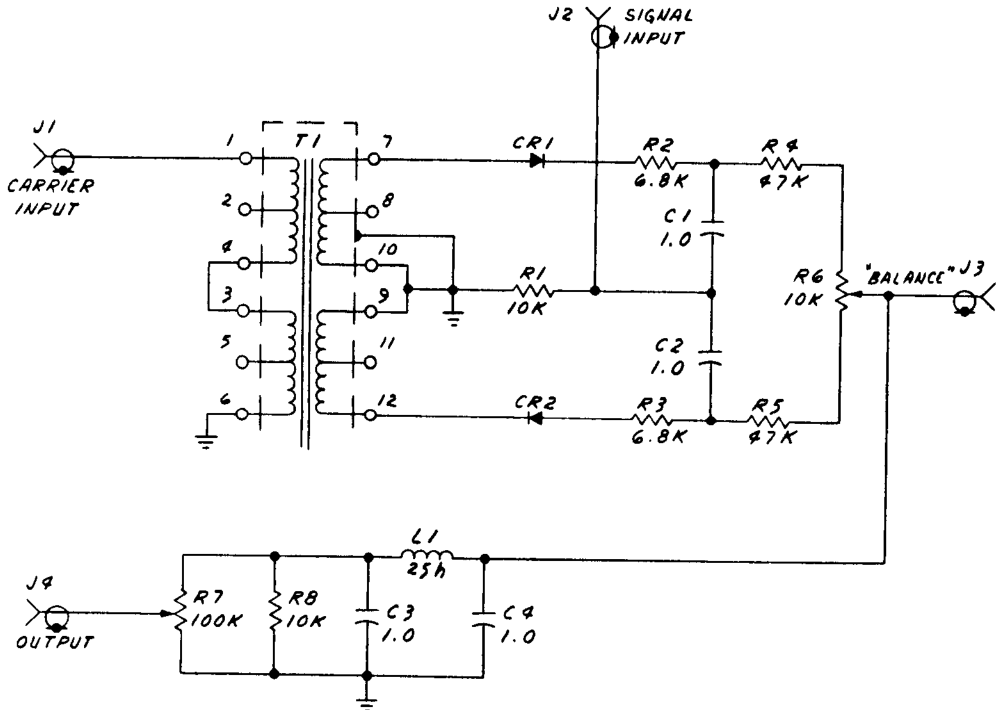
The function of the reference channel is to supply a signal to the phase sensitive detector for demodulation of the flow signal. For proper operation, the reference channel output must be in time phase with the flow signal output. Since the flow signal at the electrodes is in phase with the magnet flux, a signal derived from the flux (or, more precisely, its time derivative) is obtained from the reference winding located near the magnet jaws. As indicated in Figure 14, the voltage from the reference coil (which is in 90° time phase with respect to the flux) is first supplied to an amplifer, which prevents loading of the reference winding by the following phase shifter. This amplifier is identical with that described earlier in connection with the signal channel. Output of the amplifier is supplied to a phase shifter which is used to equalize the overall phase shift of the reference and signal amplifier channels. This adjustment is made by substituting a portion of the reference coil voltage for the probe electrode signal, and with the switch (S_1 of Fig. 14) in the "test" position, comparing the phase of the reference and flow signal channel outputs. A second amplifier-phase shifter combination is employed to introduce the required 90° phase shift to obtain a signal in phase with the magnet flux; this signal is applied when the switch is set in the "flow" position.

The reference signal is then passed through a filter similar to that employed in the signal channel, which eliminates any 400 cps harmonics which may be present because of distortion of the flux waveform. Use of this filter also makes the differential phase characteristics of the signal and reference channels much less sensitive to variations in the carrier frequency, since the major frequency dependent phase shift is contributed by the filters, which are identical. Thus with filters in both channels, a given frequency change causes the same phase shift in both channels, and only very slight differential phase shift between them. Output of the filter is raised to a level suitable for operation of the phase sensitive detector by an amplifier identical to that employed to supply the signal channel output.

d. Phase Sensitive Detector

The modulation of the carrier corresponding to the flow signal is recovered in the phase sensitive detector. By employing such a detector, information on the sense (direction) of the flow is retained. In addition, the phase sensitive detector does not respond to components of the flow signal amplifier output which are in 90^{o} time phase with its reference input. Thus, any residual "transformer" signals which may be present together with the flow signal are strongly rejected.

As indicated in Figure 17, the circuit employed is a simple two diode type. An input transformer is used in the reference channel (carrier) input to provide a balanced signal which alternately switches one or the other diode into conduction on each half cycle of the reference wave. The signal input is applied through blocking condensers. On each half cycle, current through the 6.8 K resistors is controlled by the sum of the carrier and signal voltages. If the signal voltage is zero, these two currents are equal, but because of the arrangement of the diodes, they produce opposite voltages on the two blocking capacitors. Thus no d.c. voltage appears at the midpoint of the resistance adding network R_4, R_5, R_6 . If the carrier voltage is not zero, the d.c. voltage appearing across one capacitor will be greater than that of the other, since more current flows in the diode in which the carrier signal and the input signal are in phase opposition. As a result, the sum of the voltages across C_1 and C_2 is no longer zero, and an output appears at the midpoint of the resistor adding network. The adder network output is applied to a constant K filter section, having a cutoff fre-



COMPONENTS LISTS

C1-4	1.0 µµf
CR1-2	1N658
J1-4	BNC Coaxial Connector
L1	25 h UTC HQB-12
R1	10 K
R2,3	6.8 K Welwyn
R4,5	47 K Welwyn
R6	10 K, 3 turn helipot
R7	100 K Carbon Pot
R8	10 K
T1	LS-33

NOTES:

1. All resistors are 1/2 watt, 10% carbon composition except as noted. K = 1,000 ohms

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Fig. 17 Phase Sensitive Detector

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quency of about 60 cps, which removes 400 cps and its harmonics which otherwise would appear at the output.

The preceding discussion is qualitative and intended to indicate the principle of operation. More exact analysis indicates, that provided the carrier amplitude is large compared to that of the signal, the average (d.c.) output is accurately proportional to the amplitude of the input signal and the cosine of the phase difference between the carrier and signal inputs. Thus the output amplitude is proportional to the component of the signal which is in time phase with the carrier input; quadrature components are rejected.

3. Measurements of Magnetic Fields

To improve our understanding of the magnetic field distribution in the magnet gap, and the amount of leakage flux, a series on measurements was made on the Model 1 probe.

A small "search coil" was constructed, consisting of 5 turns of #32 wire with a diameter of .16 cm. This coil was mounted in a drilled lucite rod. Since the voltage induced in the search coil was very small, the Tektronix preamplifier was employed to obtain a higher signal amplitude. By measurement of the voltage induced in the search coil, the flux linking the coil could be determined, and the average flux density over the coil area calculated.

It was of interest to examine the distribution of stray flux at various points around the probe, and at various magnet driving currents. The harmonic distortion of the induced search coil voltage is a good indicator of the onset of core saturation, since when the core saturates, a large increase occurs in the stray flux level, and the stray flux is highly non-sinusoidal. Measurements of distortion of the search coil voltage at various driving voltages were made at several positions around the core, using a Barker and Williamson model 400 distortion meter. Results of these measurements are shown in Figure 18.

It will be noted that above a driving voltage of about 50 v., the percentage distortion increases rapidly with driving voltage of the core, although the distortion of the gap flux remains nearly constant. This indicates that saturation occurs first in the portion of the core farthest from the gap. At a somewhat higher driving voltage, the distortion of the stray flux begins to increase rapidly at the "side" position. However, since the stray flux is relatively small and is mostly outside the gap, the percentage distortion of the gap flux remains relatively small up to rather high driving levels. Nevertheless, it has been felt advisable to conduct most experimental work at driving voltages of 50 v, to eliminate possible artifacts arising from the non-sinusoidal stray flux which occurs when core-saturation is present. At this driving level, the gap flux distortion is less than 1/2 per cent, and the flux density about 400 gauss.

The distribution of flux within the gap was also investigated. Measurements of the flux density were made at a variety of points. Figure 19 shows the variation of flux density with position along the center line of the flow tube. It will be noted that over most of the region spanned by the magnet jaws, the flux is relatively uniform.

4. <u>Tests of Linearity</u>

A gravity flow system has been constructed and linearity characteristics of the Model 1 probe have been investigated using saline. Figure 2 demonstrates the linear relationship between flow induced voltages and acutal flow. The highest flow rate tested was 180 cc/sec. This is greater than maximal flow in the

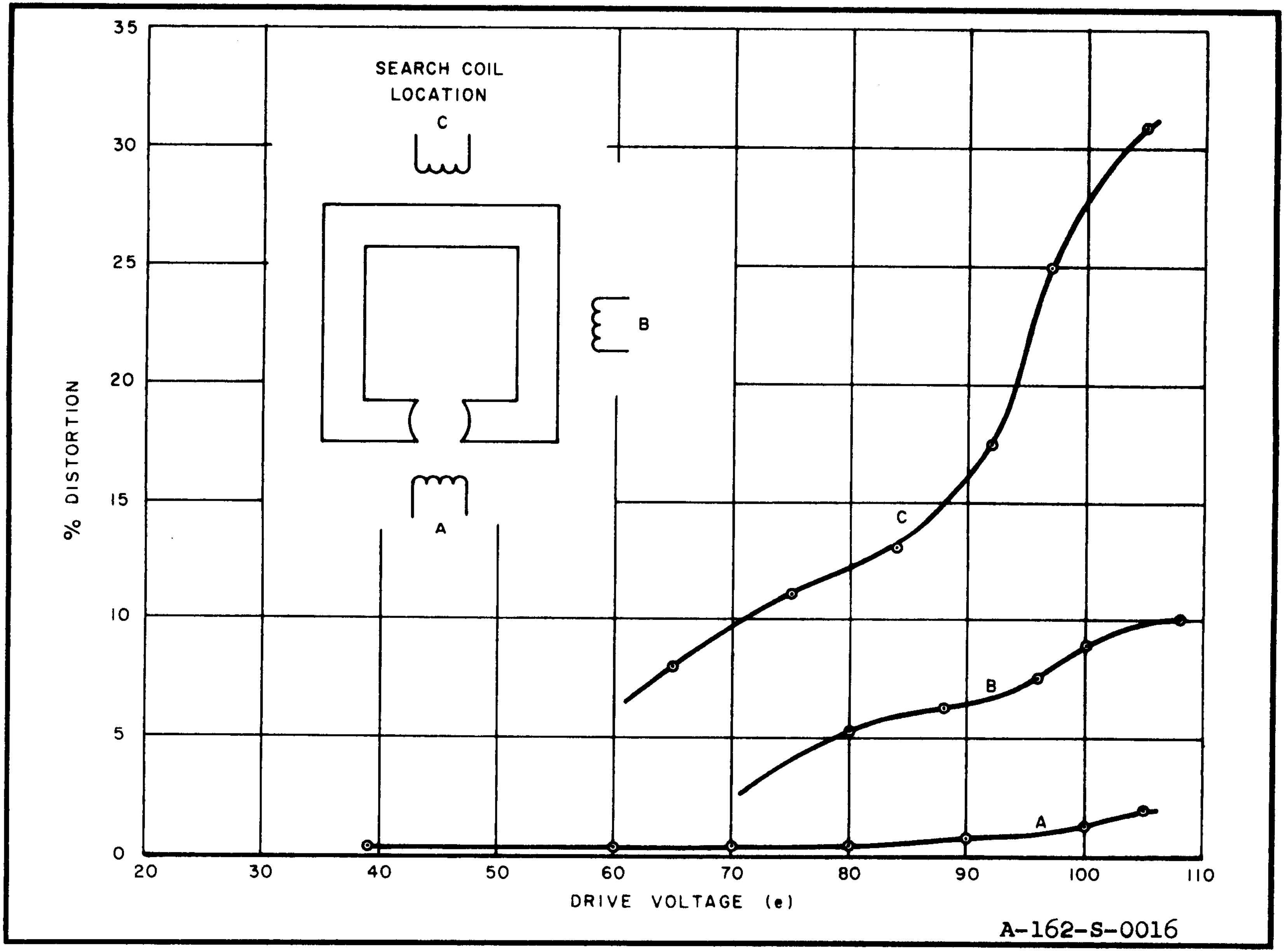

Fig. 18 Distortion of Induced Search Coil Voltages at Several Locations and Drive Levels

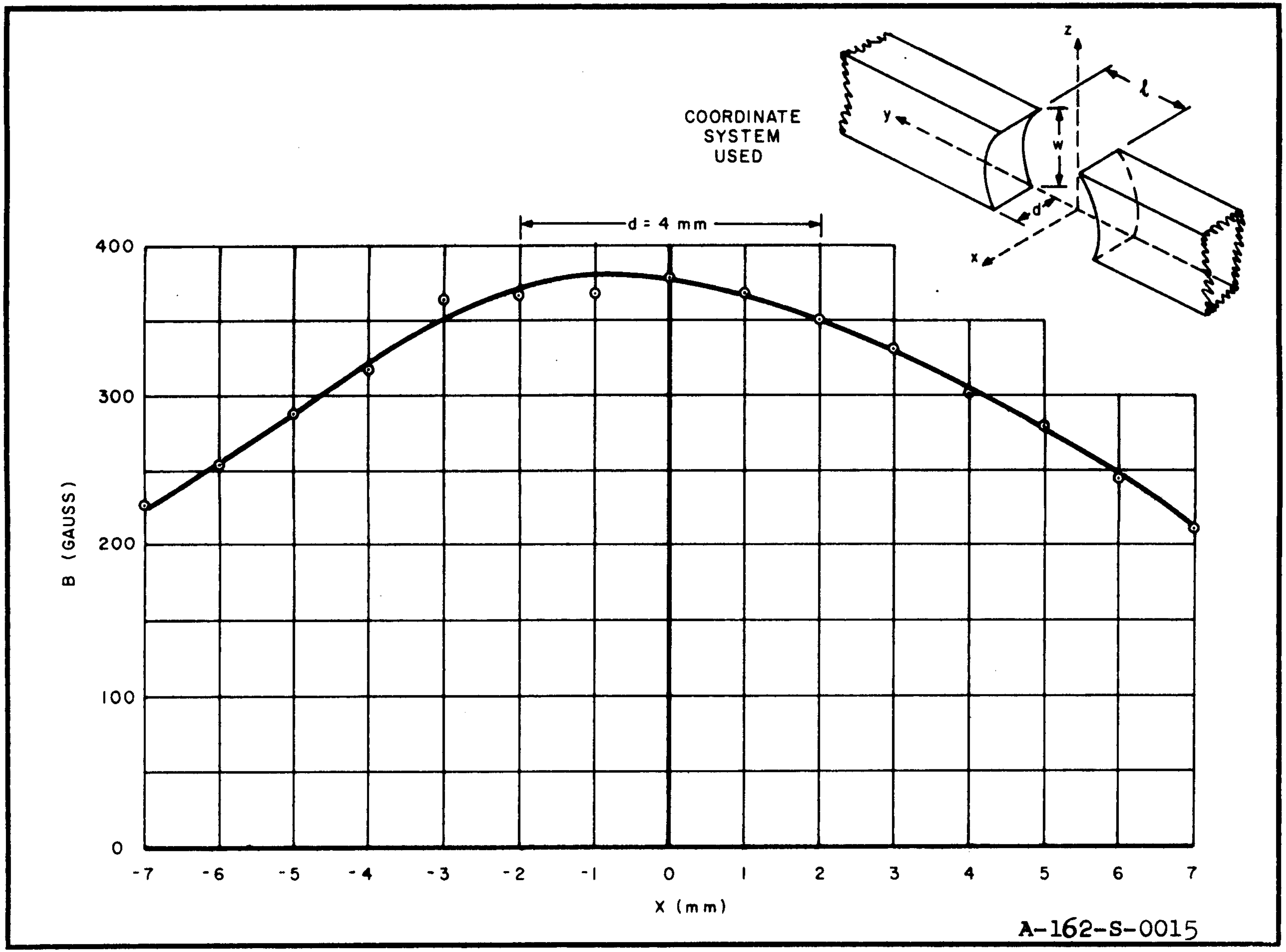

Fig. 19 Flux Density in Model 1 Magnet Gap at Several Positions Along Flow Tube Axis

dog aorta. At this flow rate, the Reynolds number is approximately 2250. The transition region between laminar and turbulent flow lies in this vicinity. These measurements are consequently encouraging though not conclusive with regard to possible effects of flow turbulence on flow meter linearity.

B. SPECIAL PROBLEMS OF IMPLANTATION

Please see pages 7 to 10.

C. RELATIONSHIP OF BLOOD FLOW TO ORGAN ACTIVITY: STUDIES OF THE AUTO-REGULATION OF THE MYOCARDIAL VASCULAR BED

There is at present little information concerning the factors that partition cardiac output and the intrinsic regulatory mechanisms that govern regional blood flow. The investigation of these parameters in the coronary vascular bed, although complicated by the mechanics of ventricular contraction, is of particular significance in view of the central importance of the coronary circulation in the maintenance of myocardial nutrition and hence the support of blood flow to all other regions.

The present study was undertaken to examine the auto-regulatory mechanisms which are brought into play when, during a period of constant cardiac work, coronary flow rates are suddenly increased or decreased by the imposition of sudden changes in coronary perfusion pressure. The relationships between coronary flow levels and myocardial work and metabolism were also examined in a preliminary fashion.

1. Methods

Studies have been conducted on thirteen mongrel dogs, weighing 15 to 25 kilograms.

A prerequisite for the performance of this study is the attainment of a relatively steady-state for extended periods of time with regard to anesthetic level, metabolism, and cardiac work in open-chest anesthetized dogs. This is necessary so that the responses of the myocardial vascular bed to imposed departures from normal flow levels can be compared with one another and utilized to construct a pressure-vs-flow curve for the same level of organ activity (in this instance, cardiac work). Since alterations in coronary flow can induce changes in cardiac output, blood pressure, and therefore the workload of the heart, the steady-state is uniquely difficult to achieve in studies of the myocardial vascular bed. The myocardial bed does have the advantage, however, that its work level can be manipulated and physically measured.

Anesthetic techniques conventionally utilized in cardiovascular investigations proved, upon study, to furnish a very unstable anesthesia level. In particular, a steady-state was not attainable utilizing intravenous pentobarbital sodium and morphine-dial-urethane. Investigation demonstrated the distinct advantages of inhalation techniques in this regard, and, after some study, fluothane (.5 to .75 per cent) with nitrous oxide (70 per cent) and oxygen (30 per cent) was chosen. This technique is readily quantitated, easily regulated, and has been shown to exert no cardiac depressant effect in the concentrations used. (Studies of anesthetic techniques to furnish stable baseline levels for physiologic investigation to be published).

Following tracheal intubation and the induction of anesthesia (.9 to 1.0 mg/kg succinyl choline), the dogs undergo left thoracotomy and pericardiotomy. Artificial respiration is maintained with a Harvard Respiratory Pump with ventilation adjusted to keep intermittently drawn blood CO_2 within the normal range. (A Beckman-Spinco CO_2 analyzer is currently being incorporated into the anesthesia system to constantly monitor alveolar pCO_2 and drive the respirator to maintain pCO_2 levels normal.

A length of circumflex coronary artery sufficient to allow cannulation is isolated, the required peripheral arteries and veins isolated, and the animal is heparinized (10 mg/kg per 30 minutes). Appropriate cannulations are then performed to connect the animal to the extracorporeal blood circuit illustrated, which has previously been filled with oxygenated heparinized blood from donor dogs. (Fig. 20)

The extracorporeal circuit developed has the following features:

1) The cannulated left circumflex artery can be perfused via line A from the left femoral artery;

2) Alternatively, through the use of the stopcock, the left circumflex artery can be perfused from the pressurized arterial blood pressure reservoir at any desired pressure level. The 20 liter buffer bottle insures minimal decay of pressure in the compressed air circuit during perfusion.

3) A Shiply-Wilson rotameter is used to record blood flow via either of these circuits. By means of a damping circuit having a time constant of .5 seconds, mean coronary flow is recorded intermittently.

4) Counter current heat exchangers (HE) proximal and distal to the rotameter make up for heat losses suffered in the extracorporeal circuit and maintain constant the temperature of blood passing through the rotameter.* The temperature of blood perfusing the coronary artery may be varied over a wide range distal to the rotameter if desired.

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* The rotameter is well known to be sensitive to temperature variations and to alterations in blood viscosity.

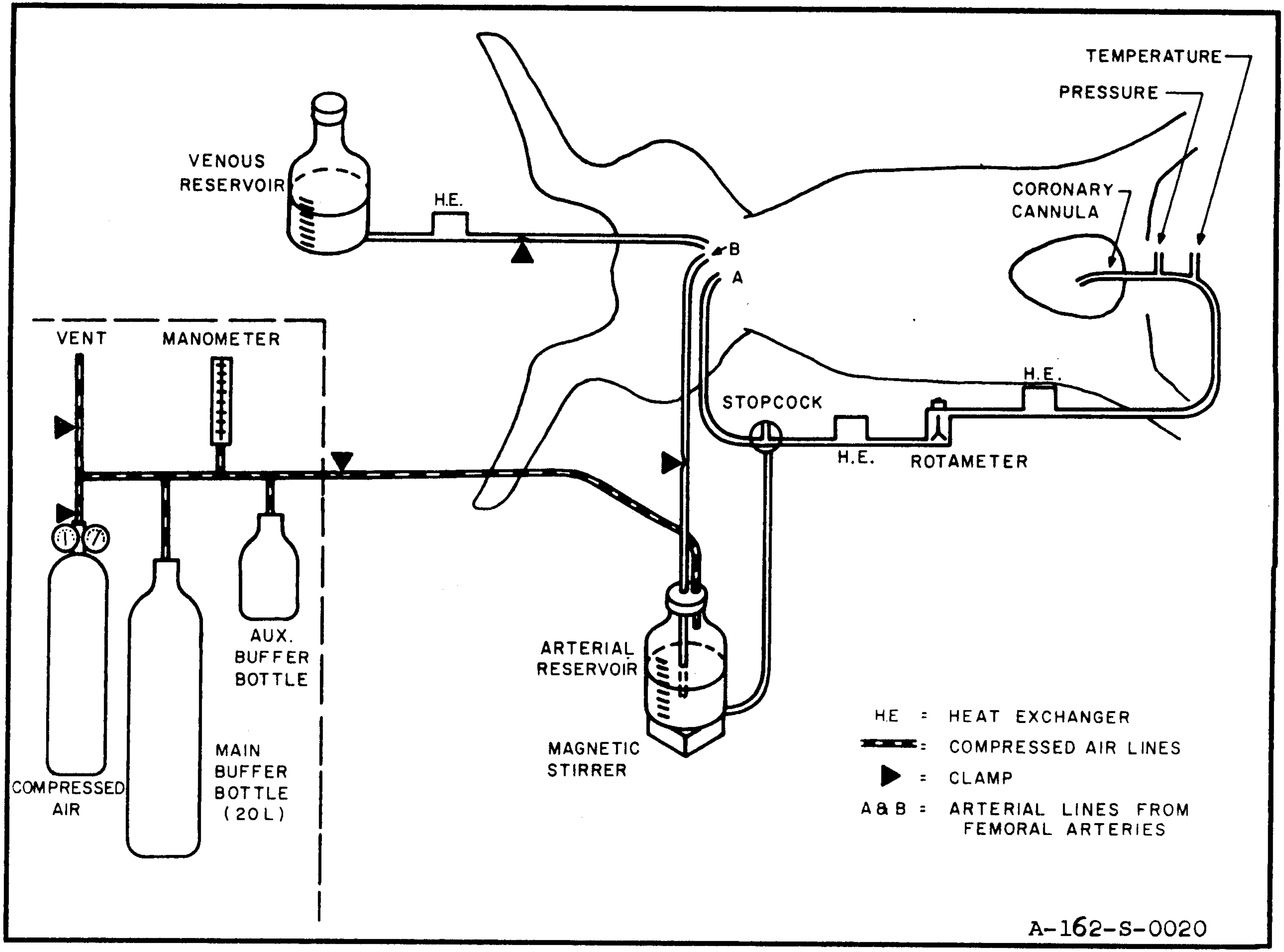

Fig. 20 Extracorporeal Circuit for Study of Auto-Regulation of Coronary Flow

5) A third heat exchanger is employed in the venous reservoir circuit to prevent alterations in the general body temperature during exchange transfusions. Body temperature is continuously monitored by a thermistor probe in the superior vena cava, which, in turn, regulates heating pads to maintain body temperature constant.

The following phenomena are continuously monitored and recorded on a multi-channel photographic oscillograph:

coronary artery perfusion pressure left ventricular pressure aortic pressure	by Statham strain gauges
coronary artery perfusion temperature body (superior vena cava) temperature	by thermistor probes

The output of the ventricular pressure channel is fed into a highly stable self-zeroing electronic integrating circuit which constantly records the integral of left ventricular systolic pressure over ten-second intervals (TTI in Fig. 21). Intraventricular pressure is a function of the tension developed by the myocardial fibers of the ventricular wall. The integral of this pressure with respect to time -- the so-called "tension-time index" -- is thus related to the work of the heart and has been shown by others to correlate well with myocardial oxygen utilization. In the absence of reliable methods for following intra-ventricular volumetric changes, the "tension-time index" appears to be the best available physical index of cardiac work. During the course of a series of steady-state "runs" where end diastolic ventricular volumes are relatively unchanged, lack of variation in the tension-time index can be viewed as a sensitive indicator of constant cardiac work.

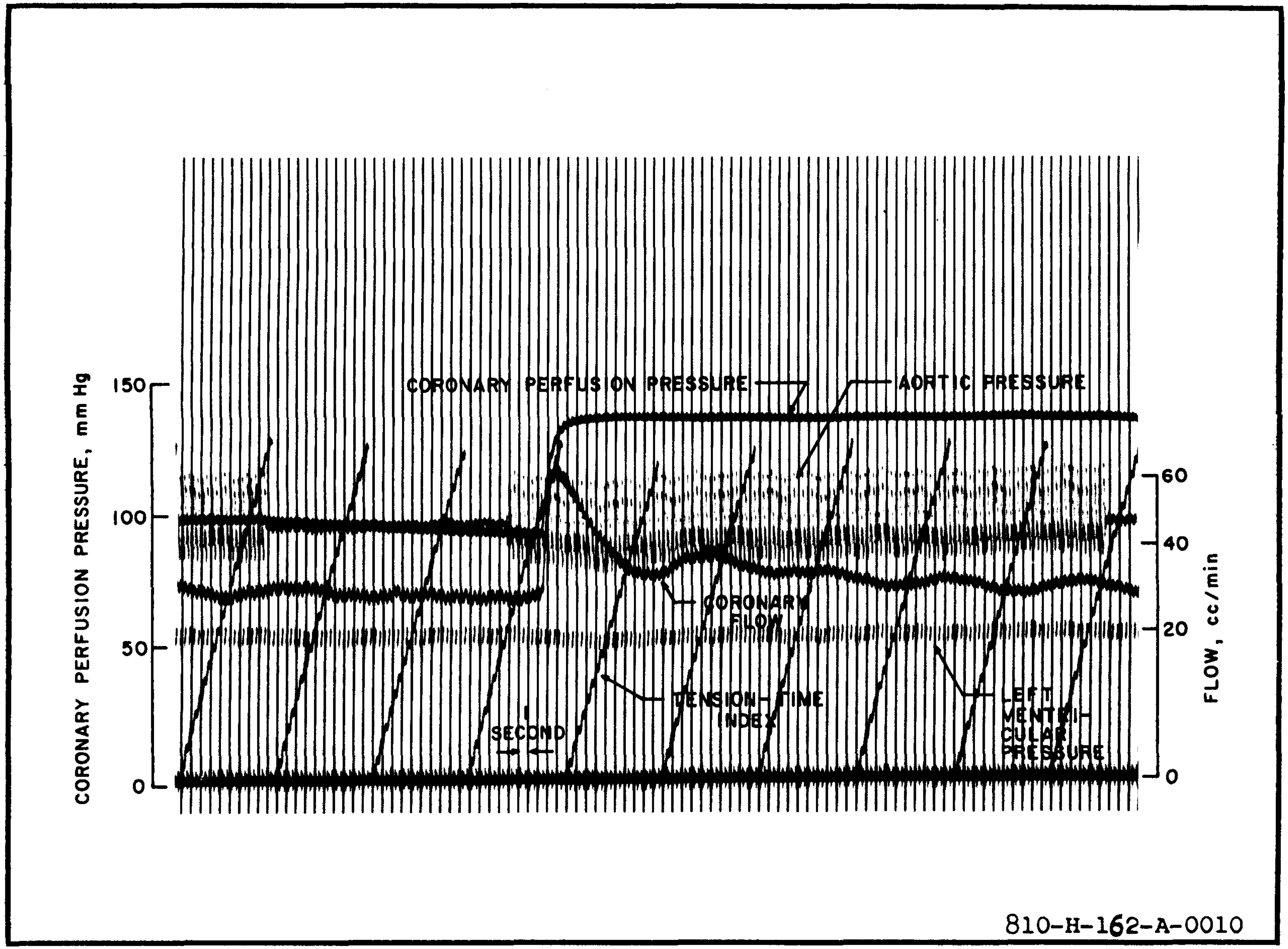

Fig. 21 Coronary Flow: Transient Response to Sudden Increment in Perfusion Pressure

The left circumflex coronary artery, by virtue of the extracorporeal circuit, is thus perfused either from the dog's own femoral artery or from the arterial blood reservoir. The blood in the arterial reservoir is obtained by bleeding from the subject's femoral artery while infusing into the femoral vein from a venous reservoir of mixed donor blood. The rates of bleeding and infusing are matched using calibrations on the two reservoirs and arterial pressure is monitored for the tolerence of the exchange. At the conclusion of the first exchange, the arterial reservoir contains 1500 cc of arterial blood and the donor blood is thoroughly mixed with that of the experimental animal. The blood in the arterial reservoir is constantly stirred by a magnetic stirrer. Hematocrits are serially drawn from the coronary perfusion line.

2. <u>Conduct of the Experiment</u>

The experiment may be performed by two techniques:

a. While the coronary artery is being perfused through the bypass circuit, the arterial reservoir is pressurized using the compressed air-buffer bottle circuit. By turning the stopcock, coronary perfusion is switched to the arterial reservoir at the predetermined pressure. Simultaneously, a femoral vein is bled into the calibrated venous reservoir to match arterial reservoir outflow and maintain blood volume in the dog constant.

The changes in coronary flow in response to the alteration in perfusion pressure are observed and recorded until flow once again becomes constant. At this time, coronary perfusion via the femoral artery is reestablished by means of the stopcock. After a return to control flow levels, another pressure step is introduced by switching to bottle perfusion once again. In this manner, the response of coronary flow to acute changes in perfusion pressure for a complete series of pressure levels from 30 mm Hg to 190 mm Hg can be studied.

b. An alternative method is to maintain the animal on reservoir perfusion during a complete pressure run, changing pressure levels in the reservoir whenever flow values have become constant. Once again, the dog is bled to match infusion. This method permits of sequentially increasing or decreasing pressure steps or the alternation of high and low pressure heads with intermediate levels. All of these methods have been utilized in this study.

After a complete series of pressure points has been recorded, the level of cardiac work may be depressed or augmented and the run repeated.

3. Results

a. Transient Response: The transient response of the coronary bed to pressure steps over a wide range of pressures has been established. A typical response is shown in Figs. 21 and 22.

Following a sudden increase in perfusion pressure from control, coronary flow increases sharply. Almost immediately, flow begins to decline in an exponential manner while perfusion pressure remains constant and elevated. Within ten to fifteen seconds, flow has returned to its former level. Not infrequently, flow values undergo a few oscillations about the former level and gradually damp out in 25-60 seconds.

Conversely, if pressure is suddenly reduced, flow falls off sharply and at once begins to rise exponentially to a constant level.

Total cardiac work, as measured by the 10-second ventricular integral, shows only slight alterations during these interventions. Changes in cardiac rate are minimal or absent.

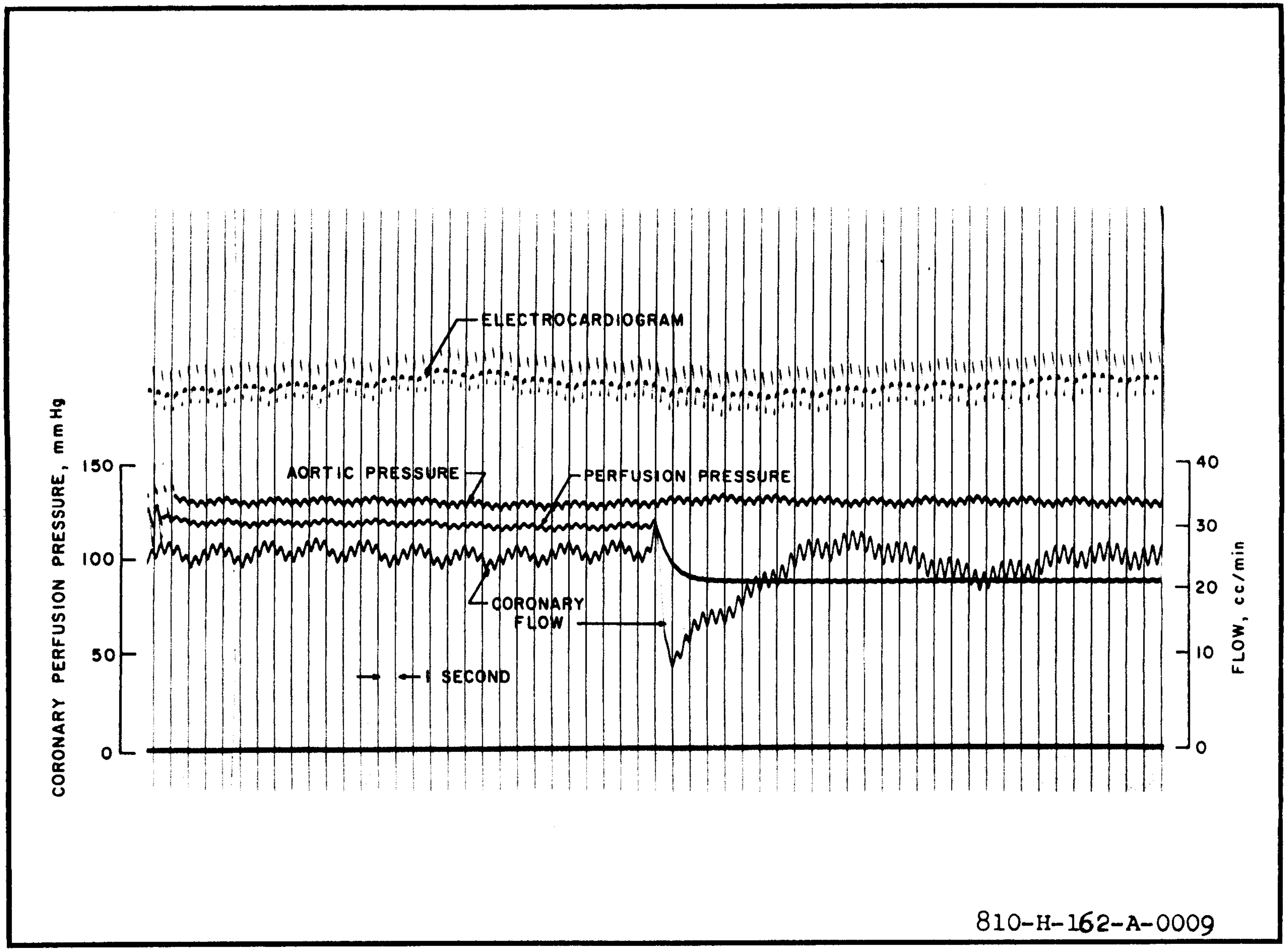

Fig. 22 Coronary Flow: Transient Response to Sudden Decrement in Perfusion Pressure

b. Post-Compensation Steady Values: The return of coronary flow values to control levels, as illustrated, occurs in "resting" heart for perfusion pressures through the physiologic range 60-70 to 120-130 mm Hg. For coronary perfusion pressures above or below this, compensation is incomplete.

If the post-compensation steady flows obtained at various pressure steps of a run are plotted against the perfusion pressures, a "steady-state pressure-flow" curve for the coronary circulation at a constant level of cardiac work is established. A representative curve obtained experimentally is shown in Fig. 23. The striking aspects of this curve are:

1. Almost complete lack of dependence of flow on perfusion pressure in the range of 60-70 to 120-130 mm Hg. (Region B)

2. Linear pressure-flow relationship below 60-70 mm Hg (region A) and above 120-130 mm Hg. (Region C)

It can be seen that the greater slope of the curve in the range of low pressure (Region A)-(vasodilatation) implies a lower resistance to blood flow than in the high pressure portion (Region C)-(vasoconstriction). Furthermore, the straight-line character of the curve in Regions A and C implies a constant resistance to flow at these pressure levels. This is in striking contrast to Region B in which resistance varies as a function of pressure to maintain flow constant.

In every experiment in which satisfactory steady states have been obtained, these same auto-regulatory mechanisms have been demonstrated. The levels of cardiac work and dimensions of blood flow have differed from subject to subject. Preliminary data from experiments in which attempts to achieve

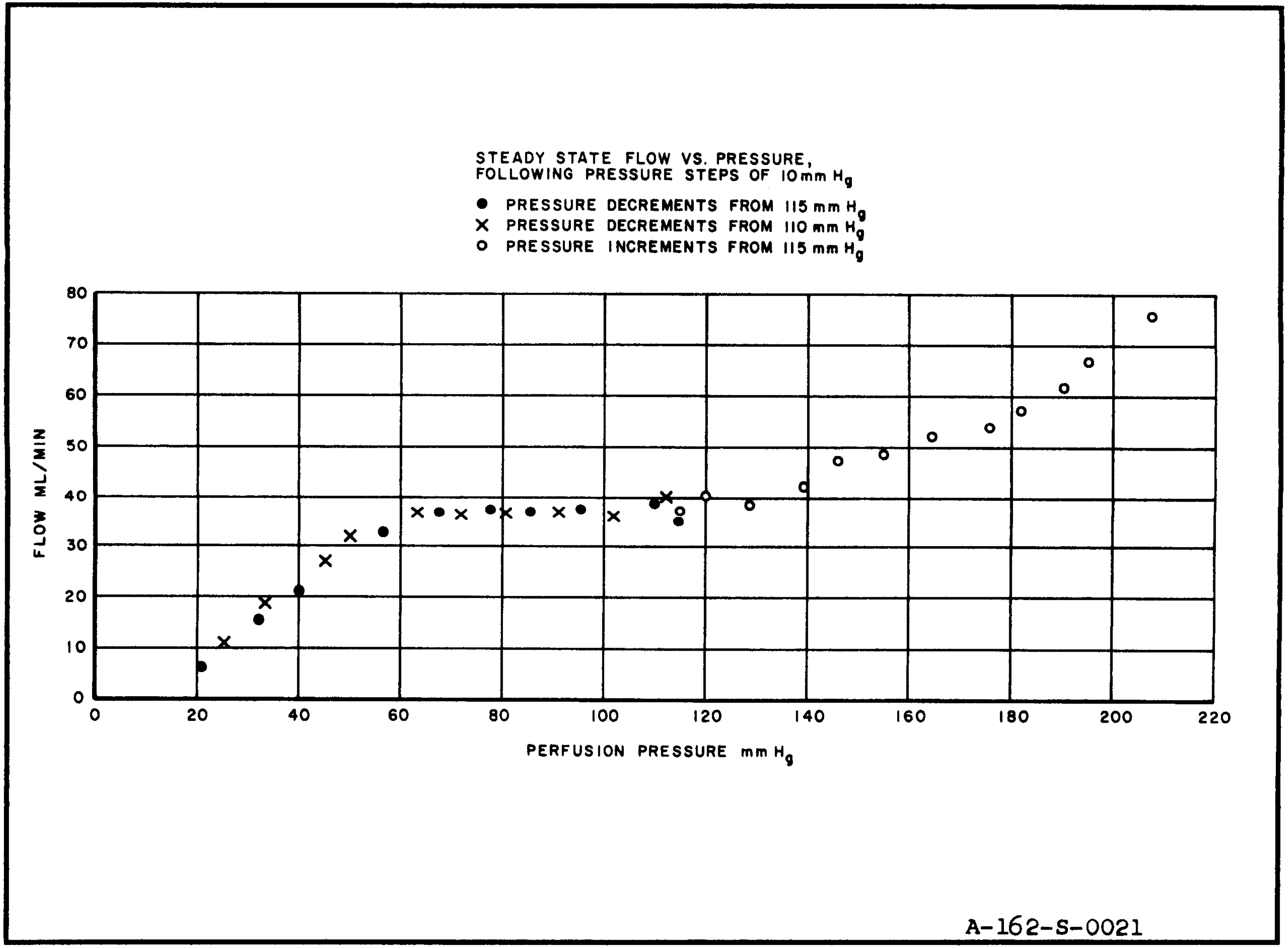

Fig. 23 Steady State: Coronary Flow Versus Coronary Perfusion Pressure

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steady augmented and depressed levels of cardiac work in the same animal demonstrate steady-state pressure-flow curves as shown in Fig. 24. Work loads and flow levels are currently being compared by the tension-time index. Comparison utilizing oxygen uptake will follow.

4. Discussion

The significance of this work in the general program and the direction it will follow are discussed on pages 10 to 17.

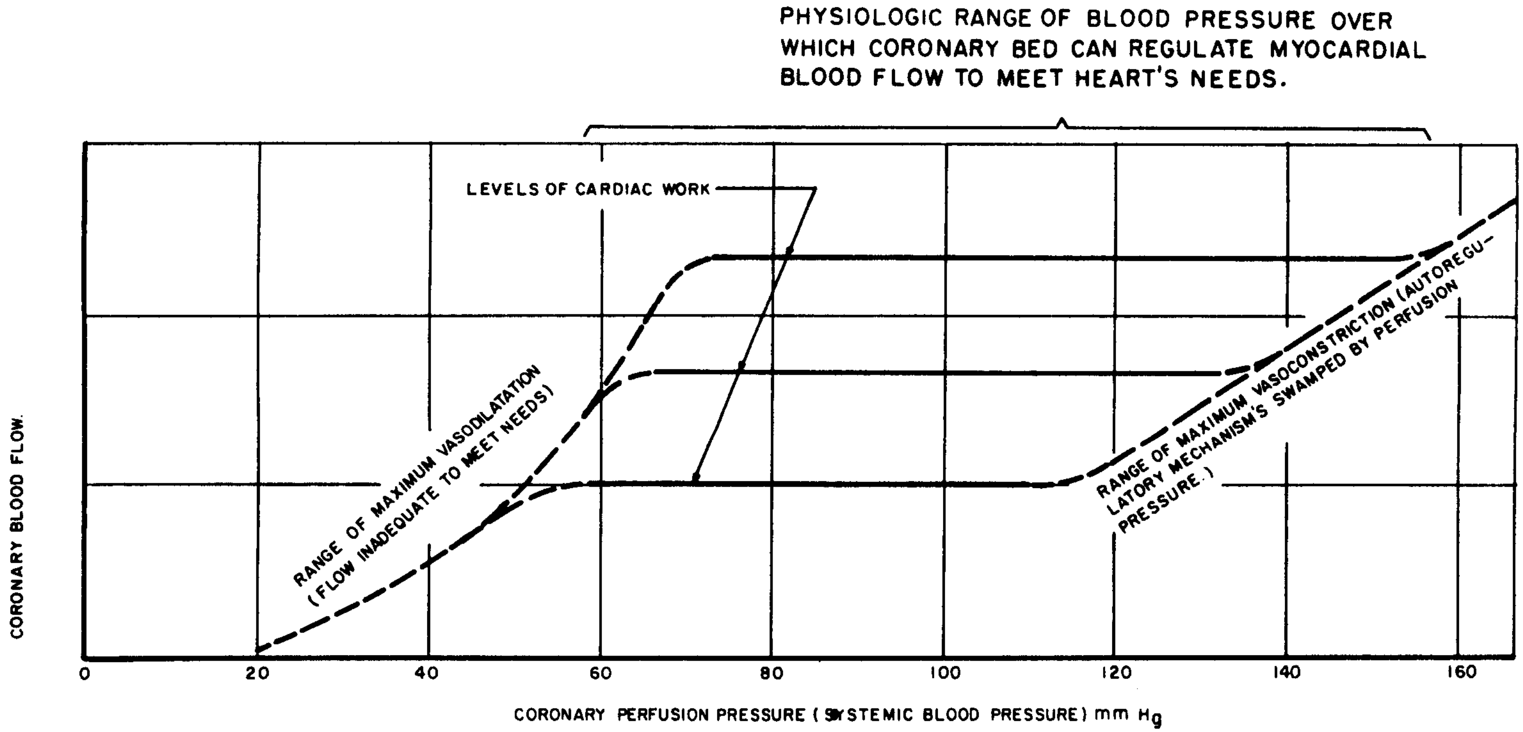

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Fig. 24 Steady State: Idealized Curves, Coronary Flow VS Perfusion Pressure for Cardiac Work Loads of Different Levels